EFFECT OF HYPERTENSION ON NERVE CONDUCTION PARAMETERS IN PATIENTS ATTENDING SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES, KULASEKHARAM.

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL

UNIVERSITY

In partial fulfillment of the requirements for the award of the degree of

M.D. PHYSIOLOGY

BRANCH V

APRIL 2015

CERTIFICATE

This is to certify that this dissertation entitled **" Effectof Hypertension on Nerve Conduction Parameters in patients attending SreeMookambika Institute of Medical Sciences, Kulasekharam"**is a bonafidework done by **Dr. L.Aswathy,** SreeMookambika Institute of Medical Sciences, Kulasekharam in partial fulfillment of the University Rules and Regulation for award of M.D.Physiology [Branch-V] under my guidance and supervision during the Academic year 2012-2015

Dr. M.S KumariSheela, **M.D**
Guide
Professor and Head
Department of Physiology
SreeMookambika Institute of
Medical Sciences
[SMIMS]Kulasekharan
[K.K.District]
Tamil Nadu - 629161

Dr. J.Kaniraj Peter, M.D
Co Guide
Professor and Head
Department of Medicine
SreeMookambikaInstitute of
Medical Sciences
[SMIMS]Kulasekharan
[K.K.District],
Tamil Nadu – 629161

Dr. RemaV.Nair, M.D.,D.G.O
Director
SreeMookambika Institute of
Medical Sciences [SMIMS]
Kulasekharan [K.K.District]
Tamil Nadu - 629161

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ABSTRACT

Effect of Hypertension on Nerve Conduction Parameters in patients attending Sree Mookambika Institute of Medical Sciences, Kulasekharam.

INTRODUCTION

The most important medical and public health issue and the single cause of death worldwide is high blood pressure.The hypertension prevalence is on a rapid increase now a days.Technological innovations are dramatically changing life style of people. Thus according Joint National Committee (JNC – VI) hypertension prevalence is 12.5% in South India. Nerve conduction is a constituent of electrophysiological test. Nerve conduction study measures duration, latency, amplitude and conduction velocity. Age and BMI are important factors that influence hypertension mediated changes in nerve conduction leading to peripheral neuropathy.

AIMS & OBJECTIVES

1.To assess the effect of hypertension on nerve conduction parameters.

2. To study the association of age and body mass index on nerve conduction parameters in hypertensive patients

MATERIALS AND METHODS

A descriptive cross sectional study of 28 normal subjects and 108 hypertensive patients of more than ten years duration with age group between 30-60 years was done and electrophysiological evaluation is done for all the subjects by computerized RMS ALERON 401 EMG/NCV/EP system. Latency (m sec), Duration, amplitude (mv), conduction velocity (mt sec) of 2 motor nerves (tibial nerve and common peroneal nerve) and 2 sensory (superficial peroneal nerve and sural nerve) of both limbs were measured.

RESULTS

The results analyzed showed that with increasing BMI, significant blood pressure changes were caused along with increasing age. Hypertension causes significant deterioration of nerve conduction variables at an earlier age.

CONCLUSION

Increasing BMI and age caused increased blood pressure and inturn causes slowing of nerve conduction variables in the control subjects.Nerve conduction variables were significantly decreased in the hypertension with increasing BMI and age; and the onset age of these variables has occurred at an younger age.

KEY WORDS

Nerve conduction study,hypertension,latency,amplitude,conduction velocity,duration.

1. Introduction

The most important medical and public health issue and the single cause of death worldwide is high blood pressure.

The situation is worse in India, since with modernization, the lifestyle is changing and diet is craving for fatty foods rather than healthy traditional food, desk bound jobs are replacing physical jobs and stressful city based life are replacing calm rural life. Probably due to the ongoing significant increase in the Indian hypertensive population; India will next become the hypertensive capital following the Diabetic Capital that it has already attained.[1] The hypertension prevalence is on a rapid increase.[2] Reliable information should be collected from across the globe from several regions that is highly essential to develop International and National health policies, which are important to control or prevent the condition.[3] Technological innovations are dramatically changing life style of people.Thus according Joint National Committee (JNC – VI) hypertension prevalence is 12.5% in South India.[4]

In 95% of cases essential hypertension is presumed to be a precursor to the onset of diabetes.[5] Hypertension defines itself as sustained elevation of BP > 140/90 mm of Hg. Diagnosis is easy and simple to treat with surplus

availability of medications, but sometimes it remains undetected, untreated and sometimes the treatment is not adequately effective.

Nerve conduction velocity test is an essential, reliable clinical test for the diagnosis of the diseases of peripheral nerves that includes peripheral neuropathies[6,7]

Nerve conduction or electoneurography is a constituent of electrophysiological test. That provides reliable and reproducible approaches to detect and characterize nerve, muscle or any neuromuscular junction diseases.[8] Nerve conduction study consist of noninvasive electrical stimulation of a peripheral nerve at one site and its non invasive measurement of the evoked response at second site in the nerve (sensory or mixed nerve conduction) or over the muscle innervated by the nerve (motor nerve conduction).

Nerve conduction study measures duration,latency, amplitude and conduction velocity. Conduction velocity and latency denote the speed of nerve impulse propagation.They are altered in disease, which causes demyelination. Amplitude denote the number of functioning fibers and it is altered in diseases causing axonal degeneration.[9]

2. Hypothesis

Age and BMI are important factors that influence hypertension mediated changes in nerve conduction leading to peripheral neuropathy.

3. Scientific Justification of the Study

After thorough review it was found that several nerve conduction studies have been done among normal individuals. Preliminary studies done by others on nerve conduction velocity based on age in healthy individuals proved that age could modulate definitely the amplitude and duration of motor & sensory nerves.[10] Study based on body mass index (BMI) showed that BMI could affect nerve conduction parameters,[11,12]and there are very limited studies across the world in nerve conduction among hypertensives. Hence there is a need to look into these parameters on hypertensives so that people can be made aware of the complications arising as an outcome of hypertension.

The theme of 2013 is High blood pressure as projected by world health organization(WHO).The definitive goal is to create greater alertness, healthybehaviour,better detection and facilitating environments.

4. Aim and Objectives

1. To assess the effect of hypertension on nerve conduction parameters.

2. To study the association of age and body mass index on nerve conduction parameters in hypertensive patients.

5. Review of literature

5.1 Introduction

5.1.1 Background and Epidemiology

Blood pressure(BP) is clinically defined as the lateral pressure exerted by the column of blood on the walls of the arteries.[13] Cardiovascular healthcare systems in India is highly pressurized by the elevated prevalence of hypertension in the common public.[14,15] Global data analysis assessing the burden of hypertension, presents 20.6% men and 20.9% women are distressed from hypertension in the year 2005 in India.[16] The rates for hypertension in percentage is projected to increase to 22.9% and 23.6%(men and women), in India by 2025.[15] Recent Indian prevalence studies in hypertension show a population ratio of 33% in urban and 25% in rural. [17-19]

Prevalence of raised BP in Indians has been shown to be 32.5% in men and 31.7% in women as estimated by the WHO in 2008.[20] Hypertension is perceived to be the third leading killer in the India; as hypertension related illness causes 1 in 8 deaths as estimated by World Health organization.[21] Thus Hypertension qualifies itself as an important area of medical research.

5.1.2 Pathophysiology of Hypertension

Pathophysiology and Molecular pathophysiology of hypertension still remains indecisive. Two to five percent of hypertensives have an essential renal or adrenal cause for their raised blood pressure, known as secondary hypertension. When hypertension has no single exclusive factorial cause the condition is termed essential hypertension.[22] Even though there are no direct causes for essential hypertension there are several risk factors that contribute towards its development. The most important of which are: surplus body weight, high dietary sodium intake, decreased physical activity, insufficient fruit and vegetable intake,excessive alcohol abuse.[23]

5.1.3 Peripheral Neuropathy

Pain perception is observed to be decreased in hypertensive subjects.[24] Rat Psychophysiological studies presented an association to hypalgesic behavior (delayed response by a limb to applied noxious stimuli such as a hot plate, electrical shock, or mechanical force) in arterial hypertension.[25-32]Zamir and Shuber illustrate that hypertensive subjects have increased tolerance to pain, that was assessed by graded electrical tooth pulp stimulation.[33] There is relatively evidence that hypertensive individuals may have peripheral neuropathy.[34-44]

Central inhibition of nerve impulses occurs in the peripheral nervous system(PNS)during peripheral neuropathy. The PNS nerves lie exterior to central nervous system innervating the limbs and organs; and is divided into Voluntary nervous system (somatic) and Involuntary nervous system (Autonomic). Incidence of peripheral neuropathy is around 2.4 that rise with age to 8%.[45]

Indian incidence of peripheral neuropathy has been documented in studies related to diabetes. There is a higher incidence of diabetes mellitus in India (4.3%)[46] when compared with the West(1-2%).[47] The incidence of Diabetic neuropathy in Indian scenario has not been epidemiologically exploited in studies; but a south Indian study presents 19.1% of type II diabetic patients present peripheral neuropathy[48], and very few study was done on the association of hypertension with peripheral neuropathy.[49-53]

What causes peripheral neuropathy?

- Autoimmunity (Inflammatory demyelinativepolyradiculoneuropathies).
- Vasculitis (Connective tissue diseases)
- Systemic illness (diabetes, uremia, sarcoidosis, myxedema, acromegaly).
- Cancer (paraneoplastic neuropathy)
- Infections (diphtheria, leprosy, lyme disease, AIDS, herpes zoster).

- Dysprotenemia (myeloma, cryoglobulinemia)
- Nutritional deficiencies and alcoholism.
- Compression and trauma.
- Toxic Industrial agents and drugs.
- Inherited neuropathies.

Oxidative stress and aging mechanisms are factors that can have definite impact on nerve conduction; the mechanisms pertaining to this have been clearly worked out with aged people[54] and in type II diabetic subjects.[55]However, not much study has been documented with hypertension.Though our study does not directly measure any aging parameters or oxidative stress parameters; references obtained will be used to back up our clinical study findings.

5.1.4 Molecular aspects of aging mechanisms on nerve conductivity

Advancing age, mediates changes in the vasculatures function and structure destruction. In precise, modification in endothelial cell functions relates to alter the expression and release of the vasoactive mediators such as nitric oxide and endothelin-1.[55]Additionally antithrombotic and vasodilatatory function of the endothelium decline with age, while inflammatory processes and oxidativestressincreases.This process is enhanced with the presence of

cardiovascular risk factor such as hypertension, appears to happen at an earlier age when compared to normal subjects[56]

Nitric oxide levels, is vital for the endothelial membrane integrity and its function.The biological levels of Nitric oxide diminishes with age leading to dysregulated vascular nature thus promoting proatherosclerotic and prothrombotic environment.[57,58,59] Different studies based on animal models, and clinical trials have accumulated evidence proving that aging augments production of reactive oxygen species (ROS) in several tissues that includes the endothelium.[60,61]

Aging induced vascular oxidative stress appears to be connected with a worldwide increased pro-oxidant setting represented by augmented expression of inducible nitric oxide synthase,[62] NAD(P)H oxidases[63] and a down-regulation of antioxidant systems such as the superoxide dismutases.[61] The increased ROS production observed with increased aging mediates a massive amount of detrimental effects. Critical functional importance of increased ROS production is to scavenge nitric oxide by superoxide (O_2^-) to synthesize peroxynitrite(ONOO-).[64,65]ONOO- is labile that easily penetrates the phoshoplipid membrane and produces substrate nitration, thereby

inactivating vital regulatory receptors,and enzymes mainly antioxidants that scavenge free radicals.[66]

The extreme decrease in nitric oxide levels during aging is aggravated by the endothelial nitric oxide synthase expression and a reduced levels of intracellular L-arginine.[67] Recent findings propose that nitric oxide production declines with aging that ultimately enhances endothelial cell apoptosis.[68]

The accelerated production of ROS giving rise to superoxide anion (O_2^-), hydroxyl radicals, hydrogen peroxide and/or reactive nitrogen species, like peroxynitrite ($ONOO^-$), observed with aging is not only thought to be implicated in nitric oxide scavenging; but is directly implicated in the upregulation of pro-inflammatory processes,like activating NF- κB (Nuclear Factor) that transcribes inflammatory factors, that activate the macrophages.[69]

Telomeres serves as important marker in cellular senescence and vascular aging[70]. Telomeres are DNA-protein complexes found at the ends of chromosomes and important for replication mechanisms.They are observed to be shortened in senescent cells as a consequence of mitochondrial ROS overproduction. In this setting, telomerase reverse transcriptase (TERT) is phosphorylated by src kinase that exports TERT from the nucleus to the cytoplasm.[71,72] During DNA replication and cell division telomeres in

chromosomes are shortened.This process is usually compensated by TERT. Aging-induces a lack of nuclear TERT activity leading to cellular senescence that occurs as a consequence of excessive telomere shortening, resulting in chromosomal instability that leads to the onset of apoptosis.

Apoptosis not only occurs in the vascular cells but can occur in the nervous cells[73]also.Thus we hypothesis these mechanisms should have a role in hypertension provoked peripheral neuropathy.

Demyelination and Neuronal cell loss are processes that occur during aging and these processes culminate into cognitive function decline in the central nervous system and these studies are well documented[74]. However age related changes in the peripheral nervous system have very little accounting as clinical and rat model studies.The impact of oxidative stress has been acknowledged to affect peripheral nerves in rat model studies[75] and clinically well documented in diabetic neuropathy[76]

5.1.5 Pathophysiology of microvascular complications and its impact on nerve conduction

Similar to our understanding of macrovascular complications, it is becoming increasingly clear that microvascular complications share a common pathophysiology and it has been well documented in diabetes.

1. Increased polyol pathway activity leading sorbitol and fructose accumulation, NAD(P)H- redox imbalances, and changes in signal transduction.
2. Nonenzymaticglycation of proteins yielding advancedglycation end-products (AGEs)
3. Activation of PKC thereby initiating a cascade of stress responses, and Increased hexosamine pathway flux [77].

The unified mechanism of tissue damage arising by combining the above mechanisms indicates hyperglycemia-mediated superoxide overproduction by the mitochondrial electron transport chain. If superoxide accumulation or euglycemia is inhibited restoration of the metabolic and vascular imbalance occurs that blocks both the initiation and progression of complications[77].

Unchecked superoxide accumulation triggers increase in polyol pathway activity, AGE accumulation, PKC activity, and hexosamine flux that

act as a feed forward system for progressive cellular dysfunction.Neural function is disorganized when neurotrophic factors that support regeneration of a nerve are lost due to metabolic and vascular disturbances.This loss on long term, can mediate apoptosis of neurons, Schwann cells and glial cells of the peripheral nervous system.[77] Depletion of nerve growth factor (NGF), neurotrophin-3 (NT-3), ciliaryneurotrophic factor, and IGF-I have been well documented[78].

5.1.5.1 Hedgehog proteins in diabetic neuropathy and its role in nerve conduction studies

The animal model study conducted calcutt and his colleagues proved that experimental diabetes induced decreased expression of dessert hedgehog protein that was accompanied with depletion of neurotrophic factors which in turn was accompanied by slowing of conduction velocities in the motor nerve and sensory nerve. This is due to the fact that dessert hedgehog protein is involved in the patterning of the peripheral nerves in developing embryo, and later involves itself in regeneration of the peripheral nerves in adult.They also showed that injection of hedgehog protein for 5 weeks restored motor and sensory nerve conduction velocities. From this study we understand that

diabetes mediated oxidative stress causes the downregulation of dessert hedgehog proteins and neurotrophic factors[77].

Increased Advanced glycation End products, and enhanced PKC activity has been well documented in hypertension also.[79,80] Though hexoseamine pathway has been documented in diabetes it could be altered in hypertension also,sincehexoseamine pathway has been correlated with insulin resistance and insulin resistance has been well documented in hypertension.[81]

5.1.6 Age and BMI

Another crucial factor is as age increases the bioavailability of nitric oxide decreases and the potential role of Angiotensin II having the vasoconstrictor activity increase. Angiotension II has been documented to increases sensence.[82]

Body fat is calculated as BMI derived from the height and weight in adult men and women. Thus it has been proved by others that higher body mass index is associated with higher incidence of mortality in aged people.[83] Based on this we hypothesized that BMI,a measure of fat could aggravate the mechanisms of aging in a more rapid manner.In people with hypertension the onset of BMI mediated aging mechanisms could occur at an earlier age.

Though many studies are going on to relate hypertension to peripheral neuropathy none of them have been able to establish a link directly because the mechanisms that occur are of very slow process and it make years to show clear manifestation as an clinical outcome in hypertension,whencompared to diabetic patients where hyperglycemia manifests these mechanisms in a faster manner leading to deleterious effects.

5.1.7 Anatomy and Physiology of Peripheral Nerve Fibers

Peripheral nervous system is made up of several constituents. The nerve roots of plexi and peripheral nerves are innervated by sensory and motor (axons). Dorsal root ganglia typically posses cell bodies, which are located local to the spinal cord. Muscle fibers near the neuromuscular junction and/or muscle spindles are the points where the nerve fibers terminate (these sites are points where muscle sensitivity to stretch is located).[84] The peripheral nerves are not only made up of the nerve fibers but they also consist of several layers of connective tissue called the endoneurium, perineurium and epineurium and they are supplied by blood vessels. [84]

Axons that are either myelinated/unmyelinated give rise to the individual nerve fibers. Schwann cells synthesize the myelin in the peripheral

nervous system, and the myelin adheres to the nerve cell membranes wrapping it in several layers.[84]

The myelin is consequently adhered by several layers of Schwann cell membrane, providing an electrical insulation to the lipid-rich myelin layer. The nodes of Ranvier appear between the Schwann cells and at these points in the nerve fiber myelin is absent. These points contains of high density of voltage-gated sodium ion channels which mediate membrane depolarization.[84]

Myelin increases the velocity of conduction in a nerve, with the distance between two adjacent nodes of Ranvier determining the velocity of the conduction in a nerve.[84]

Conduction velocity to some extent determines the nerve fibres function (Table 1). Large nerve fibres that are heavily myelinated make up mostly the somatic motor axons. Sensory nerve fibres that innervate muscle spindle (stretch) and Golgi tendon organ (tension) receptors are also heavily myelinated. Touch, proprioception and joint position sense are attributed by the Intermediate nerve fibers. Pain sensation that is sharp and the motor function that appears from autonomic preganglion are taken care of by the lightly myelinated fibers. Functions mediated by the most heavily myelinated nerve fibers tend to be affected primarily when myelin is degraded by

pathologic processes having a profound effect on the conduction rate of the nerve.[85]

Table 1: Peripheral Nerve Fiber Categories and Functions

Fiber category	Size (microns)	Speed (meters/second)	Function
Aα; Group IA and IB afferents	15	60-100	Large motor axons, Muscle stretch and tension sensory axons
Aβ;Group II afferents	12-14	30-60	Touch, pressure, vibration and joint position, sensory axons
Aγ	8-10	15-30	Gamma efferent motor axons
Aδ;Group III afferents	6-8	10-15	Sharp pain, very light touch & temperature sensation
B	2-5	3-10	Sympathetic preganglionic motor axons
C; Group IV afferents	<1	<1.5	Dull, aching, burning pain and temperature sensation

Continuous mode of propagation of electrical signal in a very slow manner occurs in unmyelinated nerve fibres represented as non-saltatory conduction, Burning pain, temperature sensation and soreness including the sympathetic, postganglionic motor nerves are conveyed by these fibers. Their speed is roughly 1 meter/second.[84]

To analyze the disorders affecting peripheral nerves and its accurate diagnosis,it is vital to remember the anatomical distribution of motor and sensory fibers as presented in Table 2.[85]

Table 2: Innervation of Clinically Important muscles

Movement tested	Main muscles	Nerve roots	Peripheral nerve
Shoulder			
Shrug (elevation)	Trapezius	C2-5	Spinal accessory
Abduction	Deltoid/supraspinatus	C5(6)	Axillary/suprascapular
External rotation	Infraspinatus/teres	C5(6)	Suprascapular
Internal rotation	Pectoralis major	C5-7	Lateral pectoral
Adduction	Latissimus/pectoralis	C6-8	Suprascapular/pectoral
Flexion	Deltoid	C5-6	Axillary/musculocut.
Elbow			
Flexion	Biceps/brachialis Brachioradialis	C5-6 C5-6	Musculocutaneous Radial
Extension	Triceps	C6-7	Radial
Wrist			
Flexion	Flexor carpi radialis Flexor carpi ulnaris	C6-7 C7-8	Median Ulnar
Extension	Extensor carpi radialis Ext. carpi ulnaris	C6-7 C7-8	Radial Deep radial
Pronation	Pronator teres	C6-7	Median
Supination	Supinator Biceps	C5-6 C5-6	Radial Musculocutaneous
Finger			
Flexion	Flexor digitorum mm.	C7-8	Median (ulnar)
Extension	Extensor digitorum	C7-8	Deep Radial
Ab- & Adduction	Interosseous muscles	C8-T1	Ulnar
Thumb abduction	Abductor pollicis br.	C8-T1	Median
Hip			
Flexion	Iliopsoas	L2-3 (L4)	Lumbar plexus
Extension	Gluteus max	L5-S2	Inferior gluteal
Abduction	Gluteus medius	L5-S1	Superior gluteal
Adduction	Adductor mm.	L2-4	Obturator

Knee			
Flexion	Hamstring	L5-S1	Sciatic
Extension	Quadriceps	L2-4	Femoral
Ankle			
Dorsiflexion	Tibialis anterior	L4-5 (S1)	Fibular (peroneal)
Plantar flexion	Gastroc/soleus	S1 (S2)	Tibial
Inversion	Posterior tibial	L5 (S1)	Tibial
Eversion	Fibular (peroneal)	L5 (S1)	Fibular (peroneal)
Great toe			
Dorsiflexion	Extensor hallucis	L5 (S1)	Fibular (peroneal)
Plantar flexion	Flexor hallucis	(S1) S2	Tibial

Stable resting membrane potential maintained by sustained ion gradients traversing the axonal membrane is critically required for nerve fiber survival. Normal membrane integrity of the constituents is required for supporting the ion gradients[84].

The neuron requires a large amount of energy to generate ion gradients and energy for transporting the moving constituents from the cell body down and up the axon. All these processes need a high blood flow rate to the nerve. Ischemia or Diminished blood flow to the nerves is poorly tolerated by them. Peripheral nerve function is mainly dependent on axonal transport.

Nerves receive innervations from the nervinervorum that are sensory or motor derived from the sympathetic nervous system. Innervations density is not consistent and likely differs with the precise nerve in question as well as

with the site along the nerve. The fibers may be associated with nerve induced pain.

5.1.8 Composition of Nerves and Nerve Action Potentials

Action potentials that arise by simultaneous stimulation of all nerve fibers is a summation of individual nerve fibers are called compound nerve action potentials (NAP).NAP's are clinically recorded routinely corresponding to large myelinated fibers from which the nerve conduction velocity can be calculated[85]

5.1.9 Action Potentials or Nerve impulses

“Nerve impulses” or “spikes” are other names that are given for action potentials. Spike trains are the chronological chain of action potentials generated by a neuron.A neuron that produces an action potential is supposed to fire.

Nerve cell’s plasma membrane is embedded with special type of voltage-gated ions channels that generate action potentials. The ion channels remain closed when the membrane potential is in resting, but they quickly open if the membrane potential increases to exactly beyond a defined threshold value. When the channels open there is depolarization in the

transmembrane voltage, and at this point sodiuminflowoccurs.This changes the electrochemical gradient, giving rise to further increasing the membrane potential. This change in membrane potential triggers additional ion channels opening, yielding a larger electric current across the cell membrane[84].

The membrane potential keeps rising till all the ion channels open up resulting in a large increase in the membrane potential. The plasma membrane polarity reverses due to the rapid influx of the sodium ion. Following this process potassium channels set off, and potassium ions flow externally reinstating the electrochemical gradient and thus returning the nerve axon to the resting state.

Hyperpolarization or refractory period is a brief negative shift that occurs after an action potential.This occurs as phenomenon of added potassium currents. The mechanism prevents action potential from reversing back in its movement.

5.1.9.1 Initiation

For the initiation of action potential the membrane voltage at the axon hillock should be raised above the threshold for firing to occur.[86]

5.1.9.2 Propagation of action potential

The action potential once formed is regenerated at regular intervals to be transmitted from the initial segment of the axon to the axon terminal.This is known as propogation of action potential.The speed of conduction of the impulse depends on myelination and diameter of the axon.Conduction velocity is more in myelinated axon and is proportionate to the diameter of the fibrer.[13]

5.1.9.3 Phases in an action potential

A typical action potential has a phase of depolarisation and a phase of repolarisation.Phase of depolarisation is recorded as asharp upward wave during which the membrane potential approaches zero and then attains a positive value.It consists of slow depolarisation to threshold (local response),rapid rising phase,overshoot and a peak.

The phase of repolarisation is recorded as downstroke during which the membrane potential returns to the resting level.It includes a rapid falling phase and a slower terminal part called after depolarisation.The phase of repolarisation is followed by an after hyerpolarisation phase during which the membrane potential undershoots and then returns back to the resting level.

The depolarisation and repolarisation phase of the action potential can be explained by sequential changes in membrane permeability to sodium and potassium leading to large fluxes of these ions across the membrane, along their gradients.Depolarisation is due to opening of voltage gated Na+ channels,causingmassive influx of sodium ions.Repolarisation is due to opening of voltage gated k^+ channels causing efflux of K^+.[13]

5.1.10 Myelin and saltatory conduction

Myelin sheaths cover the neuronal axons that mediate electrical signals that are fast and effective in the nervous system.

Membrane capacitance is reduced and membrane resistance increased by myelin sheath at the inter-node intervals.Thussaltatory movement of action potentials occurs in a fast rate from node to node.

Myelinated axons prevent the ions from entering or leaving the axons due to the presence of myelin sheaths that increases conduction velocity making the action potentials more energy efficient. With increasing axonal diameter action potential increases.[87]

Some diseases degrade myelin and impair saltatory conduction, reducing the conduction velocity of action potentials.Breakdown of myelin impairs coordinated movement in multiple sclerosis.[88]

5.1.11 Nerve conduction studies[89]

Motor and sensory nerve conduction in the humans is medically detected by NCS (Nerve conduction study). Nerve conduction velocity (NCV) is a mutual measurement observed during this study.

5.1.11.1 Medical uses

Parathesis (numbness, tingling, burning) and or weakness of the arms and legs are mainly evaluated by nerve conduction studies.

Some of the common disorders that can be diagnosed by nerve conduction studies are

- Peripheral Neuropathy
- Peroneal Neuropathy
- Spinal disc herniation
- Tarsal Tunnel Syndrome
- Ulnar neuropathy
- Carpal tunnel syndrome
- Cubital tunnel syndrome
- Gullian-Barré syndrome
- Guyon’s canal syndrome

5.1..11.2 Technique

The nerve conduction study consists of the following components

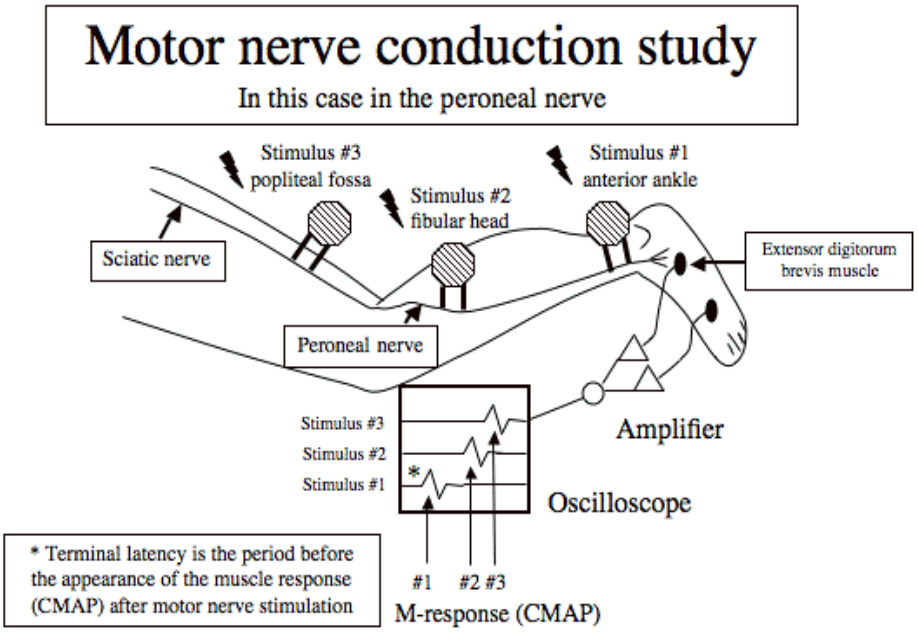
- Motor NCS
- Sensory NCS

5.1.11.3 Motor NCS

NCS of the motor nerve is done by stimulating the motor nerve and recording the response from its target muscles (Figure 2). The electrical signal recorded from stimulation of a motor nerve is called compound muscle action potential- CMAP which is generated by the muscle and it is usually large. “Terminal latency” is a term given to the amount of time taken before muscle depolarization starts.

Abnormal prolongation of this value is often of benefit in the detection of distal entrapment neuropathies.

Figure 2: Anatomical physiology of the Motor Nerve conduction study

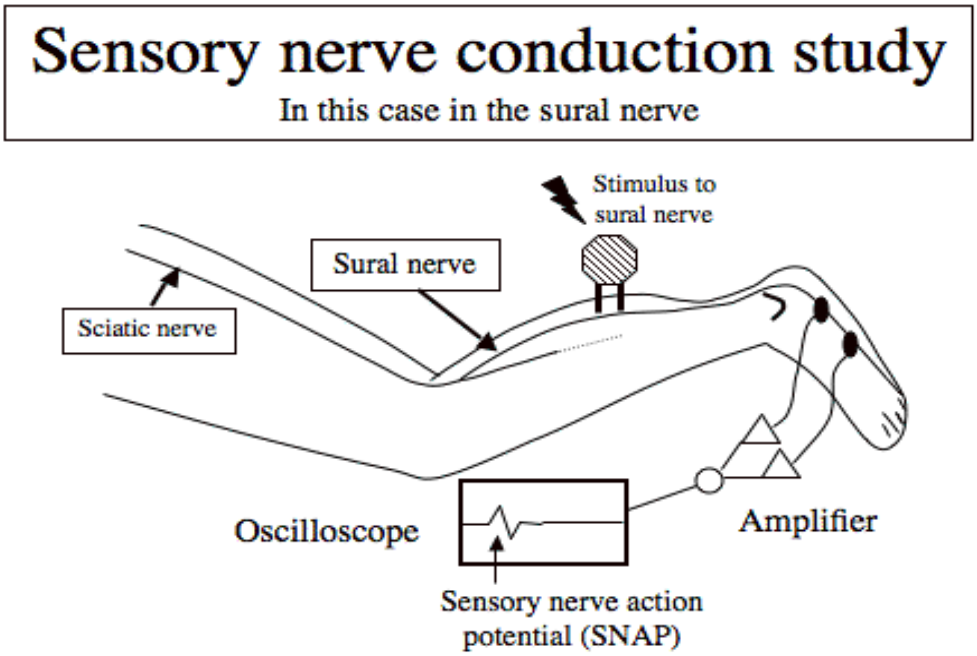


5.1.11.4 Sensory NCS

When purely sensory portion of the peripheral nerve (posterior ankle) is stimulated and the recordings are taken it is called SNAP (Figure 3).

Sensory amplitudes are much lesser than the motor amplitudes expressed in microvolt (μV),in contrast to the millisecond reading observed in the motor nerve. NCV of the sensory nerve is worked out based upon the distance between the stimulating electrodes and latency.

Figure 3: Anatomical physiology of the sensory nerve conduction study



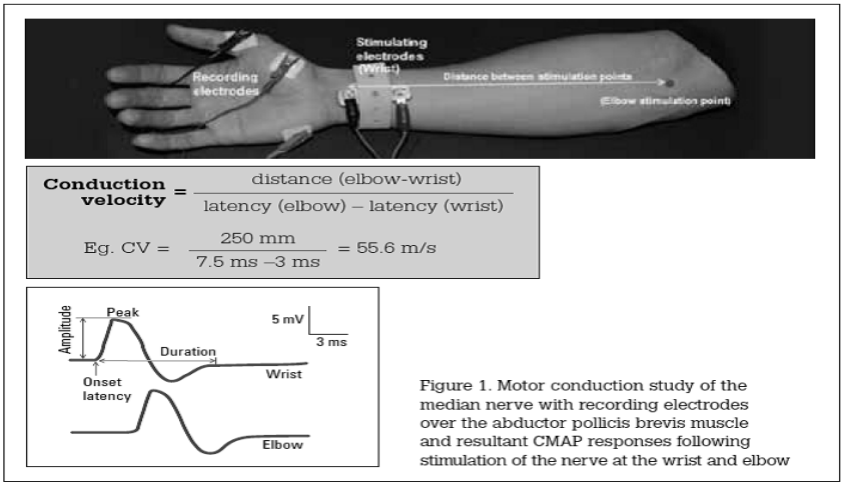
5.1.11.5 Principles of nerve conduction[89]

An electrode pair is used to stimulate impulse on one end and the other is used to record the response further down along the path of the nerve for motor nerves distally and proximally in the sensory nerves. A depolarizing square wave current is applied to the peripheral nerve to produce a compound muscle action potential (CMAP) which shows the summation of activated muscle fibers. Sensory nerve action potential (SNAP) describes the output that is summation of the electrical stimulation given to the sensory nerve.

The parameters obtained and used for interpretation include (Figure 4 shown below)

- Amplitude-From baseline to peak (reflects the number of conducting fibers and is reduced in axonal loss)
- Latency (ms)-From stimulus to onset of evoked response

Figure 4: Calculation for Nerve conduction Velocity



- Duration of response (ms)
- Conduction velocity (m/s)- Calculated from the distance between stimulation and recording points, divided by latency (reflects integrity of the myelin sheath important for impulse conduction and is reduced in demyelinating processes).

5.1.11.6 Interpretation of nerve conductions[89]

When interpreting NCS data, initial considerations are:

- Is the CMAP or SNAP amplitude is normal in size and shape or reduced?
- Is the conduction velocity normal?

5.1.11.7 Axonal loss

Axonal loss results in the reduction of compound amplitude reflection in lesser functioning axons.

If only there is axonal injury, and if the myelin sheath is not injured the remaining axons conduct with normal latencies and velocities, but if the axonal degeneration proceeds,the latencies and velocities can be slightly prolonged.It is an outcome of the loss of larger and fast conducting fibers.

Loss of myelin slows conduction which manifests as significant reduction in conduction velocities and temporal dispersion (increase in the duration). Conduction block can also occur (a reduction of area/amplitude of at least 50% at a proximal compared to a distal site of stimulation).

5.1.11.8 Normal Conduction Velocities[85]

The tables 3, 4, 5 represent the normal conduction velocity of the motor and sensory nerve fibers.Depending on the function nerves are classified according to Erlanger Gasser asmotor,sensory and secretomotor.Depending on myelination, they are classified as myelinated and unmyelinated.

Table 3: Motor Fiber types

Type	Erlanger-Gasser classification	Diameter	Multiple	Conduction velocity	Associated Muscle fibers
α	A α	13-20 μm	Yes	80-120 m/s	Extrafusal muscle fibers
β	A β	5-8 μm	Yes	4-24 m/s	Extrafusal muscle fibers

Table 4: Sensory fiber types

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity	Associated sensory receptors
Ia	Aα	13-20 mm	Yes	80-120 m/s	Responsible for proprioception
Ib	Aα	13-20 mm	Yes	80-120 m/s	Golgi tendon organ
II	Aβ	6-12 mm	Yes	33-75	Secondary receptors of muscle spindle. All cutaneous mechanoreceptors
III	Aδ	1-5 mm	Thin	3-30 m/s	Free nerve endings of touch and pressure.Nociceptorsof neospinothalamic tract. Cold thermoreceptors
IV	C	0.2-1.5 mm	No	0.5 2.0 m/s	Nociceptors of paleopsinothalamic tract. Warmth receptors

Table 5: Fiber types

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity
Preganglionic fibers	B	1-5 mm	Yes	3-15 m/s
Postganglionic	C	0.2-1.5 mm	No	0.5-2.0 m/s

Table 6 shows the normal conduction velocity of some of the peripheral nerves such as median sensory nerve,median motor nerve,ulnar sensory nerve,ulnar motor nerve,peroneal motor nerve,tibial motor nerve,sensory sural nerve.

Table 6: Peripheral Nerves

Nerve	Conduction Velocity
Median Sensory	45- 70 m/s
Median Motor	49-64 m/s
Ulnar sensory	48-74 m/s
Ulnar motor	49+ m/s
Peroneal Motor	44+ m/s
Tibial Motor	41 + m/s
Sural Sensory	46-64 m/s

5.1.12 Clinical Studies to substantiate the mechanisms explained above.

5.1.12.1 Essential hypertension is identified as a risk factor associated withmicrovascular diseases and neuropathy:

A study conducted by Anchalaet al[90] was a meta analysis paper to assess the prevalence of hypertension in India. Their results suggests 29.8% as overall prevalence of hypertension in India. Significant differences were found between the rural and urban population as 27.6% and 33.8% respectively. Regional estimates for the prevalence of hypertension were as follows: rural north, east, west and south India were 14.5%, 31.7%, 18.1%, and 21.1% respectively,whereas the urban sector presented 28.8%, 34.5%, 35.8% and 31.8%, for north, east, west and south. Overall awareness, treatment and control of BP were 25.3%, 25.1% and 10.7% for rural Indians and 42.0%, 37.6%, 20.2 for urban Indians. Thus the study in conclusion predict that 33% and 25% rural Indians are hypertensive. Of them 25% rural and 42% urban Indians are aware of their hypertensive status. Only 25% rural and 38% of urban Indians are being treated for hypertension. One-tenth of rural and one-fifth of urban Indian hypertensive population have their BP in control.

A study was done by Dhafir I. EI- Yassinet al[51] to assess the relationship between hypertension and peripheral neuropathy. The study included 25 normal subjects and 75 hypertensive patients. The study assessed nerve conduction variables of sensory nerve conduction variables of sensory nerve function, motor nerve function and also F-wave measurement. They observed statistical significance of ($p<0.05$),for the association between hypertension patients and sensory nerve conduction that presented deterioration. However, the nerve conduction studies (Median, Ulnar, Tibial) did not show much changes; whereas, in their F-wave parameter assessment the latency of the slowest F-wave was observed in the common peroneal nerve which was prolonged. From their results they interpret that smallest fibres were affected in hypertension.

Legrady P et al[91] presented that non-diabetic hypertensive patients also present the complications presented in diabetes. In their study they recruited 18 Hypertensive who were non-diabetic and 10 patients who were type 2 diabetic who also had hypertension. These two groups were compared with 11 normal healthy controls. Patients who presented hypertension were undergoing antihypertensive therapy. Cardiac autonomic neuropathy using Ewing method was detected in all patient groups. The peroneal nerve presented current perception threshold values of 250 Hz

inhypertensiveswhowere non-diabetic and the diabetics presented threshold values of 250 Hz and 5 Hz when compared to the control subjects. These values where higher than the control. Their study supports that the development of neuropathy is mainly dependent on vascular factors.

An experimental study done by Gregory et al[92] observed Behavioral, physiological and structural indices of neuropathy for a period of six months in spontaneously hypertensive and age matched normotensive rats with or without concurrent streptozotocin induced diabetes. There results predict that spontaneously hypertensive rats presented nerve ischemia, thermal hyperalgesia, nerve conduction slowing and axonal atrophy.The supernumerary Schwann cells of thinly myelinated fibers were indicative of cycles of demyelination and the remyelination was observed along with reduced levels of myelin basic protein in the nerves. Similar disorders were evident in streptozotocininduceddiabetic rats,wheremyelinated thin fibers were not observed and myelin basic protein is normal. Thus they perceive that rats presenting combined insulinopenia, hyperglycemia and hypertension provide a model for diabetic neuropathy which offers an opportunity to study the Schwann cell pathology mechanism and thus they suggest that hypertension could contribute to the pathology of diabetic neuropathy.

A clinical study was done by Shilpa K et al[93] on Auditory Brainstem responses and nerve conduction velocity in essential hypertensive subjects. Their study included 20 control subjects and 20 patients with primary hypertension in the age group between 40-60 yrs who were age and sex matched. They assessed the auditory brainstem responses (ABR) and nerve conduction velocity(NCV) of both sensory and median Ulnar nerves.They conclude that high blood pressure did cause a deficit in the auditory pathway sensory conduction in the brainstem. However their studies did not report any changes in the motor and sensory nerve conduction in the median nerve in essential hypertensive patients.

Another study reported by Edwards et al[94] presents that essential hypertension may be due to impaired nerve function. This study was done in 30 patients with unmedicated essential hypertension and 29 normotensives. They examined cutaneous sensory thresholds, median nerve (sensory and motor) conduction velocities and median nerve sensory action potential amplitudes. The authors observed that higher thresholds in cutaneous sensory thresholds and amplitudes of the sensory action potentials were smaller in the hypertensive subjects when compared to normotensives. However, they did not observe nerve conduction velocity changes in both sensory and motor nerves between the control and hypertensive subjects. Thus from these results

they infer that hypertensive patients presents subclinical axonal neuropathy of sensory afferents, thereby reducing active sensory nerve fibers without affecting myelination and this accounts for the perceptual deficits that characterize hypertension.

Another study done by Viskoperet al[95] on 52 hypertensive patients and 10 control subjects. They observed that in the hypertensive subjects nerve conduction velocity decreased with increasing blood pressure and changes in the retina. Their mean conduction velocity as observed in the hypertensive subjects was 45.4 m/sec that was ranging from 29.5 to 60 m/sec, when compared to the range of control subjects that was observed to be between 54 to 60 msec.

Though a positive correlation between hypertension and nerve conduction velocity has presented by certain authors; certain others conflict with this idea and have presented papers showing no correlation between hypertension and nerve conduction velocity as discussed below with clinical trials.

A study done by Shubangiet al[96] to assess the motor and sensory nerve conduction of the median nerve in thirty essential hypertensive patients in the age range of 40-60 years along with thirty age and sex matched controls. In

the Normotensive group the sensory nerve conduction was 60 ± 2.82 and in the hypertensive group 60.35 ± 2.78. The motor nerve conduction was observed to be 58.60 ± 4.10 in the normotensives and 57.75 ± in the hypertensives. However, the authors admit that extensive studies need to be done to confirm these findings.

Cho D Y et al[97]presents a longitudinal study of 584 hypertensive subjects (primary care patients) who were 65 years and older. These patients presented none of the 10 medical conditions known to cause peripheral neuropathy. These patients were assessed for the presence of peripheral neuropathy by the following examinations. The patients history was recorded with other following basic data like the number of hypertensive drugs being taken, systolic blood pressure, diastolic blood pressure, pulse pressure and orthostatic hypertension were measured. Also they assessed the impact of specific class of antihypertensive drugs and NSAIDs (Non-Steroidal anti-inflammatory agents) in their follow up after 3 years.History of hypertension was shown to be negatively associated with age related peripheral neuropathy, but not the hypertension variables as reported by them (Odds Ratio 0.60, 95% CI 0.40 to 0.90).They also perceive that in diabetic patients,hypertension had a protective effect on peripheral neuropathy. However, the current pulse pressure (Odds Ratio 1.03, 95% CI 1.0 to 7.05) was a positive predictor of

peripheral neuropathy in the diabetic subjects. These results are obtained by the authors after adjusting for age and BMI. In their 3rd year of assessment 287 patients using β-blocking agents (OR 3.56; 95%, CI 1.08 to 8.03) and NSAIDS (OR 2.65; 95% CI 1.37 to 5.10) also associated positively to age associated peripheral neuropathy(AAPN). They concluded stating that they could not infer why hypertension had a negative correlation with nerve conduction velocity.

5.1.12.2 Impact of Age and BMI on nerve conduction velocity

Though hypertension related studies have a conflict of interest in the hypothesis that hypertension could cause slowing in the motor and sensory nerve conduction,the leading causative factors such as BMI and age influencing the onset of peripheral neuropathy has been clearly demonstrated to have an impact on nerve conduction variables by various studies conducted in normal subjects.

Friedrich B and Fritz Bet al.[98]conducted a study on healthy individuals in the age range of 15 to 72 years. The study established the normal values for the distal and proximal segments for superficial peroneal nerve, sural nerve and posterior tibial nerve. The values were obtained from 71 healthy subjects. The authors presented electronic averaging that was used to analyze the slope

of the potentials. It was observed that distal values (lower extremities) were one tenth of those measured at the proximal end (upper extremities). The values 56.5± 3.4 m/sec was observed at the proximal segment and 46.1 ± 3.7 m/sec at the distal segment of the nerves.These values were observed as the maximum sensory conduction velocity in age range of 15 to 30 years. With increasing age of 40 to 65 years,the values showed slowing of conduction both proximally and distally (proximal conduction velocity (53.1 ± 4.6 m/sec) anddistal conduction velocity(42.5 ± 5.5 m/sec)). As observed in the arms the nerves of the legs also presented a decline in the maximum conduction velocity proximally and distally in the age range of 40-65 yrs when compared to the age range of 15 to 30 yrs. This study clearly indicates that increase in age can induce decline in nerve conduction velocity.

Another study done to assess the influence of age, height and BMI was done by Awang MS et al.[99] The methodology included 250 healthy Malaysian subjects who were hospital staff and students with no evidence of neuromuscular or musculoskeletal diseases.The subjects were subdivided based on age, BMI and height. NCV test was done in all the subjects and,the nerves tested were Median, Ulnar, Common peroneal and sural nerves (both right and left). They observed slowing of NCVs with increasing BMI in the median nerve (both sensory and motor conduction). The NCV of the motor

conduction of the Ulnar nerve also showed a similar pattern as observed in the median nerve. Whereas, the sensory nerve conduction of the ulnar nerve did not show any changes. Slowing of nerve conduction velocity with increasing BMI was also observed for the common peroneal and sural nerve. The study showed that height did not affect the nerve conduction velocity,since they could not establish slowing of nerve conduction velocity across varying heights for the nerves they studied except for the common peroneal nerve. Thus they conclude the study by saying that age and BMI do have a definite impact on nerve conduction velocity.

Though, several clinical studies have proved that increasing BMI and increasing age can slow down nerve conduction velocities in normal and hypertensive subjects, the molecular pathophysiology behind it has been least studied.We hypothesize and presume the following below said sequence of molecular pathophysiological events to occur in the control subjects that is aggravated by the presence of hypertension.

BMI is an index of body's visceral and abdominal fat overwhelming excessive fat in the body especially the abdominal fat which is an extreme and overwhelming source of free fatty acids, leading to the clinical state called

hyperlipidemia. Free fatty acids trigger the onset of oxidative stress in obese subjects and hypertensive subjects.

Slowing of the nerve conduction velocity can occur by two main mechanisms.First, the mechanism that occurs as an outcome of demyelination is observed as latency changes in NCS recordings. The second phenomenon is by axonal degeneration observed as a decline in amplitude changes in NCV tests. Both these conditions are significantly affected by oxidative stress, a factor that commonly occurs with increasing BMI and age. Hypertension is perceived to aggravate the hypothesis,because of the onset of hyperlipidemia at an earlier stage with higher BMI in hypertension.

A Study done by Brown et al[100] was a national survey carried out to evaluate relationship between BMI, blood pressure, cholesterol,and mean levels of HDL-C, hypertension and dyslipidemia. The national health and nutrition survey was carried out between 1988-1994, after adjusting for the crude age and age–specific means and proportions they analyzed multivariate odds ratio that quantified the association between hypertension, dyslipidemia and BMI. Their results established that more than one-half of the adult population were overweight (BMI 25 to 29.9) or obese (> or = 30). The prevalence of high blood pressure and mean levels of SBP and DBP increased as BMI increases

with ages that were below 60 years. Cholesterol levels also increases upto the BMI of 25,but did not rise beyond this. Rate of low HDL-Cholesterol increased and mean HDL-Cholesterol levels decreased as BMI increased. BMI, high blood pressure and abnormal lipids correlated when various factors were adjusted (age, race, education and smoking).The odds ratio were highest at the ages 20 to 39 but the trends were more apparent in the older ages. This study shows a significant correlation ($p<0.001$) between BMI, hypertension and abnormal lipids.

5.1.12.3 BMI as an Index of Body fat percentage

A cross-sectional study done by Ranasinghe et al[101] proved that BMI is an index of Body fat percentage.The study included 114 participants, in the age range of 18-83 years which were grouped into 3 age groups; young age(18-39 yrs), middle age (40-59 yrs) and elderly (>60 yrs). Bioelectrical impedance analysis was used to calculate Body Fat % and also they calculated BMI correlation and regression analysis between age-BMI and age-Body Fat %. The correlation between BMI and BF% was at $p<0.001$. From this study the authors conclude that BMI strongly correlates with Body Fat % and age and gender significantly affects BMI-BF% ($p<0.001$).

5.1.12.4 Obesity mediated oxidative stress

A study reported by Sankhlaet al[102]was designed to investigate the relationship of obesity with oxidative stress mainly mediated by increased abdominal adiposity and the study extended to assess the possible mechanism of metabolic syndrome induced by obesity. The study included 120 men and 30 women, in the age range 17-26 yrs in both genders. Generalized and abdominal obesity was analyzed by measuring BMI and waist-to-hip ratio in all the subjects. They also studied blood glucose, lipid profile, serum malondialdehyde (MDA)(a product of lipid peroxidation usually measured in humans as an indicator of oxidative stress). They also measured serum adiponectin. Their results definitely showed that serum MDA levels with increasing BMI (as per the NIH classification). Normal weight subjects when compared with obese class-2 subjects who presented abdominal adiposity had a significantly ($p<0.001$) higher serum concentration of MDA; while obese subjects without abdominal adiposity (Class-I) presented non-significant difference in the levels of serum malondialdehyde levels when compared with normal subjects. Obese subject (Class I and Class II) even presented a statistically significant ($p<0.001$) difference in the malondialdehyde levels, thus predicting the importance of abdominal adiposity to the onset of oxidative stress.

5.1.12.5 Free Fatty acid Content and turnover determine the extent of oxidative stress in obese subjects

Though abdominal obesity and hypertension link themselves through the resistance of insulin-mediated glucose disposal; abnormalities observed in the metabolism of non-esterified fatty acids are observed to play an greater role. A Study conducted by Egan et al[103] with 17 abdominaly obese subjects (11 hypertensives, 6 normotensives) was to determine whether turnover and fatty acid concentration were related to blood pressure independent of hyperinsulinemia and resistance to Insulin mediated glucose disposal. During fasting and during euglycemichyperinsulinemia at 10 and 40 mU/ml/min, the following analyses were carried out such as glucose utilization, fatty acid concentration, and fatty acid turnover. The protocol was repeated with another 30 subjects also who had a wide range of risk factors and also blood pressure data, glucose and fatty acid measurements during an insulin tolerance test. The 17 obese hypertensive subjects whose blood pressure was assessed correlated significantly ($p<0.001$) with the free fatty acid concentration and turnover but not with glucose disposal. The correlation remained statistically significant after insulin and index of sensitivity to insulin mediated glucose disposal were statistically controlled. The results suggest that blood pressure is related to the effects of insulin on fatty acid metabolism. The mechanism

suggest that insulin resistant hormone lipase increases blood pressure by increasing fatty acid concentration and turnover in hypertensivies.

The elevated free fatty acid can induce elevation of blood pressure through oxidative stress which has been experimentally proved by a study done by Wang et al.[104] The study assessed the possible mechanism of oxidative stress in the high free fatty acids (FFAs)-induced hypertension. The male Sprague-Dawley rat models were subdivided into three groups; Group I(Control),Group II(Free fatty acid group-induced by 4 hour infusion of intralipid and heparin),Group III(Supplemented N-acetyl cysteine antioxidant along with the intralipid and heparin infusion).

Blood pressure measurements were recorded for all the rats, Endothelium dependent vasodilatation(EDV)/Endothelium independent vasodilatation was measured in an organ chamber. ROS levels (Reactive oxygen species), nitrotyrosine, GSH (Glutathione), NO_2^-/NO_3^- levels were measured in plasma. eNOS (Endothelial Nitric oxide synthase) mRNA was measured in endothelial cells by real time PCR. The results were as follows (i) Blood pressure was elevated in the Group II rats (FFA group following 4 hour infusion of intralipid and heparin) and this was statistically significant ($p<0.001$) when compared to Group I (control). However group III

(Antioxidant supplemented group with intralipid and heparin infusion) did not show any changes in the levels of blood pressure. (ii) EDV in response to Ach was impaired ($p<0.001$) in Group II rats. Whereas, there was no significant changes observed in the Group III rats when compared to Group I control rats. (iii) Likewise NO_2^-/NO_{3-}, Glutathione levels was significantly decreased ($p<0.001$) when compared to Group I and Group III rats that presented no significant changes.This study shows that high free fatty acid levels induce oxidative stress that mediates potential destruction of nitric oxide causing imbalance between Angiotensin II and Nitric oxide causing the BP to deviate. Thus they suggest FFA plays an important role in causing elevation of BP through oxidative stress.

It has already been discussed above that hypertension can induce subclinical axonal neuropathy and this might be caused by the prevailing hyperdyslipidemia that induces oxidative stress and oxidative stress converts nitric oxide to a more potent peroxynitrite that can trigger neuronal death via the activation of PARP(poly-ADP-ribose polymerase) enzyme.Oxidative stress can mediate demyelination. These processes cause amplitude and latency changes. Further clinical and experimental studies to prove this discussion are given below.

A clinical study by Kassemet al[105]shows that hypertriglyceridemia can induce peripheral neuropathy in neurologically asymptomatic patients. Their study recruited 24 patients (21 males and 3 females having triglyceride level above 300 mg/dl who had no neurologic complaints and no other causes of Peripheral neuropathy. These patients under went Nerve conduction studies. Their distal motor and sensory latencies (DL), motor or sensory conduction velocities (CV), and motor or sensory amplitudes were measured from the peroneal, posterior tibial, sural, median and ulnar nerves. Their results showed that 70.8% patients had a significant delay in the distal latency of the sural nerves, 66.7% significant delay in the distal latency of the sensory median fibers, 54.2% subjects showed a decrease in the motor conduction velocity of posterior tibial nerve and 33.3% patients presented a significant decrease in the sensory conduction velocity of the sural nerve. Amplitudes was not observed to be affected. The study concluded by saying that hypertriglyceridemia can affect conduction parameters in peripheral nerves which is suggestive of early peripheral neuropathy.

Thus hypertriglyceridemia in hypertension mediates the onset of oxidative stress and is the prime culprit for nerve damage.

In hypertension there are not much clinical studies relating oxidative stress to peripheral nerve damage. However, studies which describe that antioxidant therapy can improve nerve conduction variables in diabetes has been proved and these are indirect studies that prove oxidative stress is main the factor in the destruction of the peripheral nerves.

A study presented by Farvidet al[106] is a double blind randomized placebo-controlled clinical study that was designed to assess if micronutrients supplementation could improve neuropathy indices. In their study 75 type 2 diabetes patients were assigned to three treatment groups.They received single treatment for a period of 4 months as daily supplement. Group I or named as group MV received zinc (20 mg), magnesium (250 mg), vitamin C (200 mg) and E (100 mg). Group II or named as group MVB received the above minerals and vitamins along with vitamin B1 (10 mg), B6 (10 mg), biotin (200 mg) and folic acid (1 mg); Group III or named as Group P served as the placebo. Out of the 75 patients 67 patients completed the study. Neuropathic symptoms were derived based on MNSI questionnaire.Neuropathy symptoms improved from 3.45 to 0.64 ($p<0.001$) in group MVB from 3.96 to 1.0 ($p<0.001$) in group MV and from 2.54 to 1.95 in placebo after the study period of 4 months. The clear outcome of this study is that micronutrient supplementation can improve diabetic neuropathy symptoms.

A study presented by Thiyagaranet al[107] assessed the impact of lifestyle modification and lifestyle modification combined with yoga on BP and heart rate of individuals who presented with prehypertension (systolic BP 120-139 mm Hg and/or diastolic BP 80-90 mm Hg). Volunteers were in the age range of 20-60 years of both genders without any known cardiovascular disease and were randomized to either LSM (n= 92) or LSM + yoga group (n =92). Both the groups were assessed for age, waist circumference, physical activity, BP and fasting plasma glucose and lipids before and after the therapy. After therapy BP and Heart rate significantly reduced in both groups. Reduction was 6 mm Hg in the LSM + yoga group whereas 4 mm Hg in the LSM group. In addition 13 prehypertensives became normotensives in the LSM + yoga group, and 4 in LSM group. The study presented that aerobic exercise in any format can benefit in the reduction of BP and this is achieved by reducing the visceral and abdominal fat through these exercises.

A Study presented by Tutuncu et al[108] examined the effect of vitamin E, on electrophysiological parameters in patients with diabetic peripheral sensorymotor polyneuropathy.21 subjects with type 2 diabetes were enrolled for double-blind randomized placebo-controlled study (11 patients were supplemented vitamin E 900 mg for 6 months 11 patients served as placebo). Fasting glucose, HbAI, postprandial glucose and NCV parameter were

assessed at the basal state and after 6 months. Glycemic index did not show any significant changes during the study. However, nerve conduction in 2 of the 12 studied electrophysiological parameters showed improvement after 6 months in patients treated with vitamin E. The changes were obvious in the median motor nerve fibers, and tibial motor nerve fibers. Nerve conduction velocity of the median nerve fiber ($P = 0.0019$) and tibial motor nerve distal latency ($P < 0.0284$) improved significantly after 6 months of vitamin E supplementation. This study proves that oxidative stress is a primary factor and it can improve nerve conductivity.

An experimental study presented by Nagamatsuet al.[109] determined whether lipoic acid could reduce oxidative stress in diabetic nerves and improve neuropathy. They used streptozotocin-induced diabetic neuropathy (SDN) rats and evaluated the efficacy of lipoic acid on nerve blood flow (NBF), electrophysiology and indexes of oxidative stress in peripheral nerves of rats is made diabetic with streptozotocin. At 1 month after onset of diabetes in age-matched control rats, lipoic acid was administered at the doses of 20, 50 and 100 mg/kg intraperitoneally five times per week the onset of diabetes. The results showed a 50% reduction of nerve blood flow in the diabetic rats. Lipoic acid did not have effect on the nerve blood flow of normal nerves but improved in diabetic rats in a dose-dependent manner. After 1 month of

treatment with 100 mg of lipoic acid supplementation in the diabetic rats showed normal nerve blood flow, significant restoration of reduced glutathione when compared to SDN rats and alpha-tocopherol-deficient nerves.Conduction velocity of the digital nerve was reduced in diabetic rats that improved upon Lipoic acid supplementation. The study thus proved that lipoic acid improves the complications induced by diabetes by reducing the oxidative stress. Thus they suggest this drug may have potential effect in the treatment of human diabetic neuropathy.

A Study presented by ReljanovicMet al[110] was a prospective PLA-controlled, randomized, double-blind study for a period of two years.Type 1 and Type 2 diabetics were randomly assigned to three treatment regimens

(i) 2 x 600 mg of TA (TA 1200 mg)

(ii) 600 mg of TA and placebo (PLA)(TA 600 mg)

(iii) Placebo and Placebo (PLA).

A trometamol salt solution of TA of 1200 mg or 600 mg or PLA was intravenously administered once daily for five consecutive days, before enrolling the patients in oral treatment phase. The study carried out the following Neuropathy disability (NDS) score which measured the severity of the diabetic neuropathy. NCV of sural sensory nerve conduction velocity,and

the tibial (motor nerve conduction velocity, motor nerve distal latency were assessed.The final data analysis took consideration of 65 patients (TA 1200 n=18, TA 600 n=27; PLA n= 20). At baseline there were no statistical differences observed in these groups. After 24 months statistical difference was observed between the TA and PLA for sural SNCV +3.8±4.2 m/s in TA 1200, +3.0±0.3 m/s in TA 600, -0.1±-4.8 m/s in PLA($p<0.05$ for TA 1200 and TA 600 vs PLA); sural SNAP +0.6±2.5 microV in TA 1200, +0.3/-1.4 microV in TA 600, -0.7±15. microV in PLA ($p= 0.075$ for TA 1200 vs PLA and $p<0.05$ for TA 600 vs PLA), tibial MNCV ±1.2±3.8 m/s in TA 1200, -0.3/-5.2 m/s in TA 600, 1.5±2.9 m/s in PLA ($p<0.05$ for TA 1200 vs PLA). No significant differences were observed between the groups after 24 months in the tibial motor nerve distal latency and NDS. In this study TA appeared to have a beneficial effect on several attributes of nerve conduction.

A meta analysis study conducted by Rosenfeldt et al[111] was to assess the efficacy of coenzyme Q10 for hypertension and to assess its overall efficacy and consistency of therapeutic action and side-effect incidence.12 clinical trials were selected (362 patients) comprising three randomized controlled trials, one crossover trials (n=120), SBP in the treatment group was 167.7 mm Hg and 151.1 mm Hg after a decrease of 16.6 mmg Hg ($p<0.001$), but there was no significant changes observed in the placebo group. DBP

presented an 8.2 mm Hg decrease($p<0.001$) (103 mm Hg before treatment and 94.8mm Hg after treatment) there was no significant changes observed in the placebo group. In the cross-over study (n=18), SBP decreased by 11 mm Hg and DBP by 8 mm Hg ($p<0.001$) with no significant change with placebo. In the open label studies (n=214) mean SBP and DBP was 162 and 97.1 before treatment and it was observed to be 148.6 mm Hg and 86.8 mm Hg after treatment. SBP presented a decrease of 13.5 mm Hg and DBP presented a decrease of 10.3 mm Hg ($p<0.001$). Thus the study concluded that coenzyme Q10 has potential to lower SBP to 17 mm Hg and DBP to 10 mm Hg without significant side effects in the hypertensive patients.

An experimental study presented by Sims-Robinson et al[112] was to determine age-related deficits in the peripheral nervous system and the role of oxidative stress in this process. They used microarray technology to assess the functional and morphological changes in the normal wild-type mice and copper/zinc superoxide dismutase-deficient (Sod1(-/-)) mice, a mouse model of increased oxidative stress. Sod1(-/-) mice exhibited peripheral neuropathy phenotype with normal sensory nerve function and deficits in motor nerve function. Their data suggest that decrease in cholesterol synthesis that is vital to myelin formation, correlates with the structural deficits in axons, myelin and the cell body of motor neurons.Such deficits appeared after 30 months in

the Sod1(+/+) mice whereas in Sod 1 (-/-) mice it appeared at 20 months compared with mice at 2 months.The study demonstrated that the functional and morphological changes within the peripheral nervous system in the model of increased oxidative stress were manifested at an earlier age and resemble the deficits observed during normal aging.

A study presented by Coppey LJ et al[113] assessed the effect of antioxidant supplementation on diabetic rats vascular and neural function. They fed the diabetic rats either with 0.5% alpha-lipoic acid as diet supplement or hydroxyethyl starch deferoxamine (HES-DFO) by weekly intravenous injections at a dose of 75 mg/kg. The antioxidant treatment significantly improved diabetes induced decrease Endoneurial blood flow(EBF), acetylcholine-mediated vascular relaxation in arterioles and sciatic nerve motor nerve conduction velocity. The treatment also reduced the production ofsuperoxide content and peroxynitrite.Treating diabetic rats with alpha-lipoic acid prevented diabetes induced increase in thio-barbituric acid-reactive substances and improved lens glutathione levels. But however, diabetes induced sciatic nerve conjugated diene levels were not restored by either alpha-lipoic acid or HES-DFO. Sciatic nerve Na+K+ATPase activity and myo-inositol levels was partially restored by alpha lipoic acid but not by HES-DFO. The authors perceive that diabetes-induced oxidative stress and

the generation of superoxide is partially responsible for the development of diabetic vascular and neural complications.

A study conducted by Hernandez-Ojeda et al[114] evaluated the oral impact of ubiquinone in diabetic polyneuropathy and the role of lipid peroxidation (LPO) and nerve growth factor (NGF-β). They conducted a double-blind placebo-controlled clinical trial.The patients were randomized to ubiquinone (400 mg) or placebo daily for 12 weeks. Main outcomes were clinical scores, NCV studies, LPO, NGF-β and safety assessment with the mean age of the 56 years, 22% males and 78% females, mean evolution of Type 2 diabetes was 10.7 years). Experimental group vs control group was found to show significant improvement in neuropathy symptoms score from 2.5 +/- 0.7 to 1 +/- 0.8($p<0.001$), neuropathy impairment score (5.5 +/- 4 to 3.1 +/- 2.6 $p<0.001$), sural sensory nerve amplitude (13.0 +/- 6.1 to 15.8 +/- 5.1 μV $p = 0.049$), peroneal motor nerve conduction velocity (39.7 +/- 5.0 to 47.8 +/- 4.9 m/s p- 0.047) and ulnar motor nerve conduction velocity (48.8 +/- 6.8 to 54.5 +/- 6.1 m/s, $p= 0.046$). LPO reduced significantly in subjects treated with ubiquinone vs placebo (16.7 +/- 8.6 and 23.2 +/- 15.8 mmol/ml, respectively) with $p<0.05$ and NGF-β did not change; and no drug-related adverse reactions were reported in the study. This study reveals that 12 week ubiquinone therapy improved clinical outcomes, nerve conduction

parameters by reducing oxidative stress in diabetic polyneuropathy patients without any adverse reactions.

An experimental study done by Pacher et al[115] was to evaluate reactive oxygen species triggered activation of nuclear enzyme Poly-ADP-ribose polymerase(PARP), which in turn contributes cardiac and vascular dysfunction in various diseases like hypertension,diabetesetc.Retired Breeder spontaneously hypertensive rats and apo E knockout mice were treated for 20 weeks with PARP inhibitor PJ34. Treatment with PARP inhibitor did not influence blood pressure and cardiac hypertrophy in SHR(spontaneously hypertensive rats) but it did improve Ach-induced Nitric Oxide-mediated vascular relaxation. Thus it is known from this study that PARP activation leads to pathogenesis of endothelial dysfunction associated with hypertension and aging

All these studies point to one common mechanism that can also be true in hypertension mediated peripheral nerve degeneration.The mechanism is that obesity and hypertension induce high levels of free fatty acids that in turn increase the levels of oxidative stress there by depleting nitric oxide and converting it to peroxynitrite, that in turn activates PARP to induce axonal degeneration.

Likewise oxidative stress could also cause demyelination process leading to the culmination of all these processes into peripheral neuropathy. Thus with this following mechanistic hypothesis this study was proceeded.

6. Materials and Methods

6.1 Study Design:

This study was designed as descriptive cross sectional study.

6.2 Study Setting:

This study was conducted in the research laboratory in the Department of Physiology in Collaboration with Department of Medicine of SreeMookambika Institute of Medical Sciences,Kulasekharam,KanyakumariDistrict, Tamilnadu.

6.3 Time of Study:

This study was done during the time period between April 2013 and July 2014 for over a period of 16 months.

6.4 Sample size calculation:

The sample size of this study was determined based on the studies published in literature, which have shown that the prevalence rate of hypertensive neuropathy in hypertension is 25%.

The formula used is n = (Za + Zb)2 (P1Q1 + P2Q2)/(P1-P2)2

Where Z_α : z value for level of significance

Z_β : z value for power of the test

P_1 : Proportion in sample 1

Q_1 : 100- P_1

P_2 : Proportion in sample 2

Q_2 : 100-P2

Z_α : 1.98 for 5% level of significance

Z_β : 0.86 for 80% power

Hence by applying the formula

n = $(1.98 + 0.86)^2$ (25 x 75) + (60 x 40)/ (25-60)2

= (8.1)(1875+2400)/ 35 x 35

=34627/1225

= 28.26

6.5 Study groups:

The study was planned to meet the aims and objectives by dividing the subjects into two groups (28 control subjects and 108 hypertensive subjects) after considering the inclusion and exclusion criteria. Each groups are further subdivided based on BMI and age.The detail of the study groups is given below in figure 5.

Figure 5:Description of the study groups

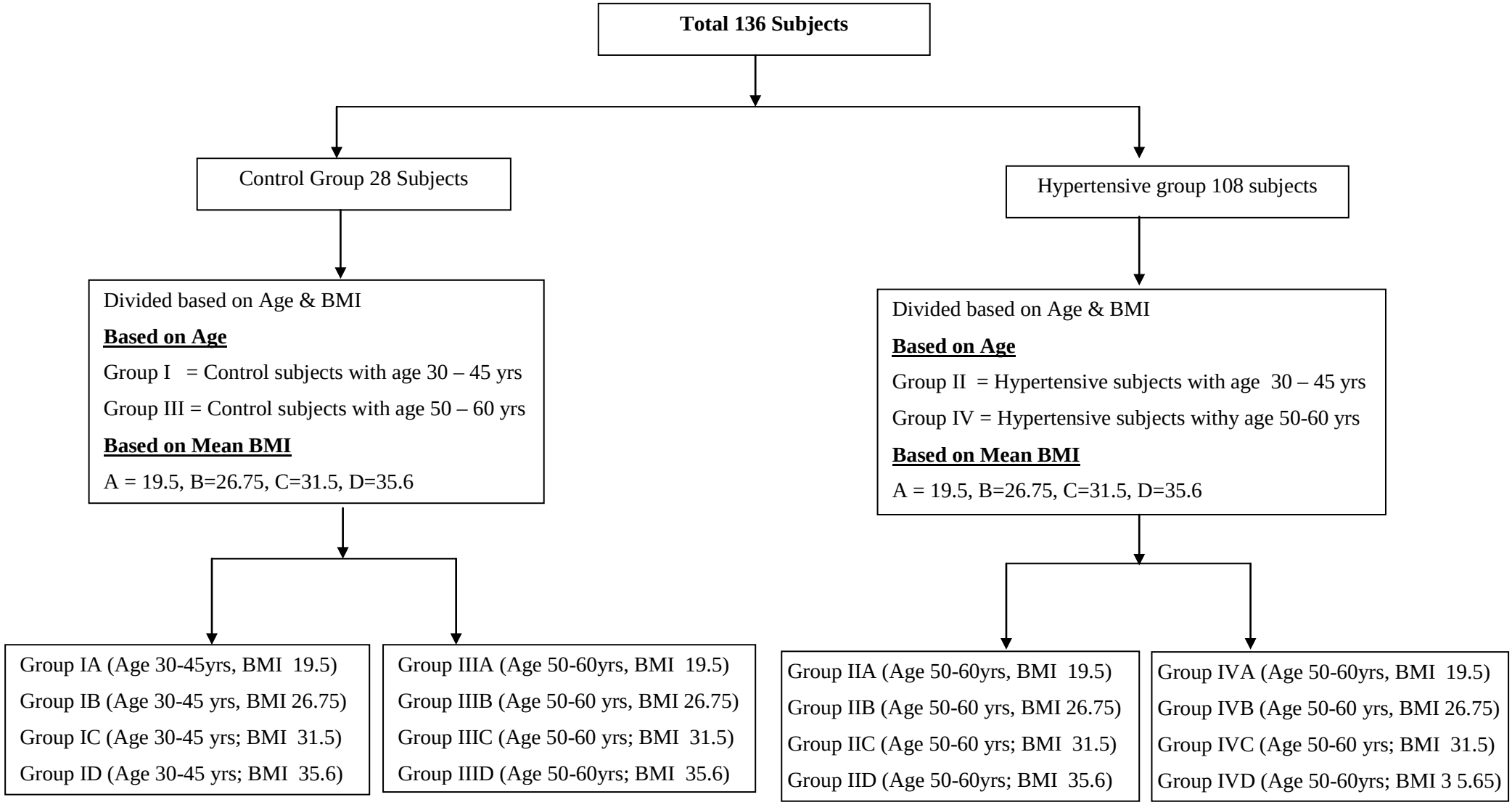


Table 7: Grouping of the control volunteers and hypertensive patients based on age, BMI and Height.

Table 7a: Control and hypertensive volunteers in the age range of 30-45, Mean BMI, and Mean Height

Group 1 A (Mean of Control subjects with age between 30-45,Mean BMI 19.5 with a mean height 168.23)			
Grouping	Age	BMI	Height
Group I a (N =1)	30	19.5 ± 0.26	168.23 ± 2.3
Group I b (N =1)	35	19.5 ± 0.27	168.23 ± 2.4
Group I c (N =1)	40	19.5 ± 0.25	168.23 ± 2.5
Group I d (N =1)	45	19.5 ± 0.28	168.23 ± 2.2

Group 1A determines the Mean of Control subjects with age between 30-45 years and Mean BMI 19.5 with a mean height 168.23 which is subdividedinto Group Ia (control subject with age 30 years with BMI 19.5 ± 0.26), Group Ib (control subject with age 35 years with BMI 19.5 ± 0.27),Group Ic (control subject with age 40 years with BMI 19.5 ± 0.25) and Group Id (control subject with age 45 years with BMI 19.5 ± 0.28). N= Number of subjects in each group.

Group II A (Mean of Hypertensive subjects with age between 30-45,Mean BMI 19.5 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group II a (N = 3)	30	19.5 ± 0.26	168.23 ± 2.3
Group II b (N = 3)	35	19.5 ± 0.27	168.23 ± 2.4
Group II c (N = 3)	40	19.5 ± 0.25	168.23 ± 2.5
Group II d (N = 3)	45	19.5 ± 0.28	168.23 ± 2.2

Group II A determines the mean of Hypertensive subjects with age between 30-45 years, Mean BMI 19.5 and a Mean height 168.23 which is subdivided into Group II a (Hypertensive subject with age 30 years with BMI 19.5 ± 0.26), Group II b(Hypertensive subject with age 35 years with BMI 19.5 ± 0.27),Group II c (Hypertensive subject with age 40 years with BMI 19.5 ± 0.25),Group II d (Hypertensive subject with age 45 years with BMI 19.5 ± 0.28). N= Number of patients in each group.

Group I B (Mean of control subjects with age between 30-45 Mean BMI 26.75 and a mean height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group I e (N =1)	30	26.75 ± 0.26	168.23 ± 2.3
Group I f (N =1)	35	26.75 ± 0.27	168.23 ± 2.4
Group I g (N =1)	40	26.75 ± 0.25	168.23 ± 2.5
Group I h (N =1)	45	26.75 ± 0.28	168.23 ± 2.2

Group I B determines the mean of control subjects with age between 30-45years and mean BMI 26.75 and a mean height of 168.23.Group Ie (control subject with age 30 years with BMI 26.75± 0.26),Group If (control subject with age 35 years with BMI 26.75 ± 0.27),Group Ig (control subject with age 40 years with BMI 26.75± 0.25),Group Ih (control subject with age 45 years with BMI 26.75 ± 0.28).N= Number of subjects in each group.

Group II B (Mean of Hypertensive subjects with age between 30-45 Mean BMI 26.75 and a Mean height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group II e (N =3)	30	26.75 ± 0.26	168.23 ± 2.3
Group II f (N=3)	35	26.75 ± 0.27	168.23 ± 2.4
Group II g (N =3)	40	26.75 ± 0.25	168.23 ± 2.5
Group II h (N =3)	45	26.75 ± 0.28	168.23 ± 2.2

Group II B determines the mean of Hypertensive subjects with age between 30- 45 years, mean BMI 26.75 and a mean height of 168.23. Group II e (Hypertensive subject with age 30 years with BMI 26.75 ± 0.26, Group II f (Hypertensive subject with age 35 years with BMI 26.75 ± 0.27), Group II g (Hypertensive subject with age 40 years with BMI 26.75 ± 0.25), Group II h (Hypertensive subject with age 45 years with BMI 26.75 ± 0.2). N= Number of patients in each group.

Group I C (Mean of Control subjects with age between 30-45 BMI 31.5 and a mean height of 168.23)			
Grouping	Age	BMI	Height
Group I i (N =1)	30	31.5 ± 0.26	168.23 ± 2.3
Group I j (N =1)	35	31.5 ± 0.27	168.23 ± 2.4
Group I k (N =1)	40	31.5 ± 0.25	168.23 ± 2.5
Group I l (N =1)	45	31.5 ± 0.28	168.23 ± 2.2

Group I C determines the mean of Control subjects with age between 30-45 years,BMI 31.5 and a mean height of 168.23.Group I I (control subject with age 30 years with BMI 31.5 ± 0.26),Group I j(control subject with age 35 years with BMI

31.5 ± 0.27),Group I k (control subject with age 40 years with BMI 31.5± 0.25),Group I l (control subject with age 45 years with BMI 31.5 ± 0.28).N= Number of subjects in each group.

Group II C (Mean of Hypertensive subjects with age between 30-45 BMI 31.5 and a mean height of 168.23)			
Grouping	Age	BMI	Height
Group II i (N =3)	30	31.5 ± 0.26	168.23 ± 2.3
Group II j (N =3)	35	31.5 ± 0.27	168.23 ± 2.4
Group II k (N =3)	40	31.5 ± 0.25	168.23 ± 2.5
Group II l (N =3)	45	31.5 ± 0.28	168.23 ± 2.2

Group II C determines the mean of Hypertensive subjects with age between 30-45years,BMI 31.5 and a mean height of 168.23 .Group II i (Hypertensive subject with age 30 years with BMI 31.5 ± 0.26),Group IIj (Hypertensive subject with age 35 years with BMI 31.5 ± 0.27),Group II k(Hypertensive subject with age 40 years with BMI 31.5 ± 0.25),Group II l (Hypertensive subject with age 45 years with BMI 31.5 ± 0.28.N= Number of patients in each group.

Group I D (Mean of Control volunteers with age between 30-45 Mean BMI 35.65 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group I m (N =1)	30	35.65 ± 0.26	168.23 ± 2.3
Group I n (N =1)	35	35.6 ± 0.27	168.23 ± 2.4
Group I o (N =1)	40	35.6 ± 0.25	168.23 ± 2.5
Group I p (N =1)	45	35.6 ± 0.28	168.23 ± 2.2

Group I D determines the mean of Control subjects with age between 30-45 years ,mean BMI 35.65 and a Mean height 168.23. Group I m (control subject with age 30 years with BMI 35.65 ± 0.26), Group I n (control subject with age 35 years with BMI 35.65± 0.27), Group I o (control subject with age 40 years with BMI 35.65 ± 0.25), Group I p (control subject with age 45 years with BMI 35.65 ± 0.28). N= Number of subjects in each group.

Group II D (Mean of Hypertensive subjects with age between 30-45 Mean BMI 35.65 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group II m (N =3)	30	35.65 ± 0.26	168.23 ± 2.3
Group II n (N =3)	35	35.6 ± 0.27	168.23 ± 2.4
Group II o (N =3)	40	35.6 ± 0.25	168.23 ± 2.5
Group II p (N =3)	45	35.6 ± 0.28	168.23 ± 2.2

Group II D determines the mean of Hypertensive subjects with age between 30-45 years and mean BMI 35.65 and a mean height 168.23. Group IIm (Hypertensive subject with age 30 years with BMI 35.6 ± 0.26), Group II n(Hypertensive subject with age 35 years with BMI 35.6 ± 0.27),Group II o (Hypertensive subject with age 40 years with BMI 35.6 ± 0.25), Group II p (Hypertensive subject with age 45 years with BMI 35.6 ± 0.28).N= Number ofpatients in each group.

Table 7 b: Control and hypertensive subjects with age 50-60, mean BMI, and Mean Height.

Group III A (Mean of Control volunteers with age between 50-60 Mean BMI 19.5 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group III a (N =1)	50	19.5 ± 0.26	168.23 ± 2.3
Group III b (N =1)	55	19.5 ± 0.27	168.23 ± 2.4
Group III c (N =1)	60	19.5 ± 0.25	168.23 ± 2.5

Group III A determines the mean of Control subjects with age between 50-60 years, BMI mean 19.5 and a mean height 168.23. Group III a (control subject with age 50 years with BMI 19.5± 0.26), GroupIII b (control subject with age 55 years with BMI 19.5 ± 0.27), Group III c (control subject with age 60 years with BMI 19.5 ± 0.25). N= Number of subjects in each group.

Group IV A (Mean of Hypertensive subjects with age between 50-60 Mean 19.5 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group IV a (N =4)	50	19.5 ± 0.26	168.23 ± 2.3
Group IV b (N =5)	55	19.5 ± 0.27	168.23 ± 2.4
Group IV c (N =6)	60	19.5 ± 0.25	168.23 ± 2.5

Group IV A determines the mean of Hypertensive subjects with age between 50-60 years and mean BMI 19.5 and a mean height 168.23. Group IVa (Hypertensive subject with age 50 years with BMI 19.5 ± 0.26), Group IV b (Hypertensive subject with age 55 years with BMI 19.5 ± 0.27),Group IV c

(Hypertensive subject with age 60 years with BMI 19.5 ± 0.25).N= Number of patients in each group.

Group III B (Control volunteers with age between 50-60 BMI 26.75 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group III d(N =1)	50	26.75 ± 0.26	168.23 ± 2.3
Group III e (N =1)	55	26.75 ± 0.27	168.23 ± 2.4
Group III f (N =1)	60	26.75 ± 0.25	168.23 ± 2.5

Group III B determines the Control subjects with age between 50-60 years ,BMI 26.75 and a mean height 168.23. Group III d (control subject with age 50 years with BMI 26.5 ± 0.26), Group III e (control subject with age 55 years with BMI 26.5 ± 0.27), Group III f (control subject with age 60 years with BMI 26.5 ± 0.25).

Group IV B (Mean of Hypertensive subjects with age between 50-60 BMI 26.75 and a Mean of height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group IV d (N=4)	50	26.75 ± 0.26	168.23 ± 2.3
Group IV e (N=5)	55	26.75 ± 0.27	168.23 ± 2.4
Group IV f (N=6)	60	26.75 ± 0.25	168.23 ± 2.5

Group IV B determines the mean of Hypertensive subjects with age between 50-60 years, BMI 26.75 and a Mean of height of 168.23.Group IV d (Hypertensive subjects with age 50 years with BMI 26.5± 0.26), GroupIV e (Hypertensive subject

with age 55 years with BMI 26.5 ± 0.27), Group IV f (Hypertensive subject with age 60 years with BMI 26.75 ± 0.25). N= Number of patients in each group.

Group III C (Control subjects with age between 50-60 Mean BMI 31.5 and a Mean height 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group III g (N =1)	50	31.5 ± 0.26	168.23 ± 2.3
Group III h (N =1)	55	31.5 ± 0.27	168.23 ± 2.4
Group III i (N =1)	60	31.5 ± 0.25	168.23 ± 2.5

Group III C determines the control subjects with age between 50-60 years,mean BMI 31.5 and a mean height 168.23. Group III g (control subject with age 50 years with BMI 31.5± 0.26), GroupIII h (control subject with age 55 years with BMI 31.5± 0.27), Group III i (control subject with age 60 years with BMI 31.5± 0.25)

Group IV C (Mean of Hypertensive subjects with age between 50-60 Mean BMI 31.5 and a Mean of height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group IV g (N =4)	50	31.5 ± 0.26	168.23 ± 2.3
Group IV h (N =5)	55	31.5 ± 0.27	168.23 ± 2.4
Group IV i (N =6)	60	31.5 ± 0.25	168.23 ± 2.5

Group IV C determines the mean of Hypertensive subjects with age between 50-60 years mean BMI 31.5 and a mean of height of 168.23).Group IV g (Hypertensive subjects with age 50 years with BMI 31.5 ± 0.26), GroupIV h (Hypertensive subject with age 55 years with BMI 31.5 ± 0.27),Group IV

i(Hypertensive subject with age 60 years with BMI 31.5 ± 0.25).N= Number of patients in each group.

Group III D (Mean of control subjects with age between 50-60 Mean BMI 35.65 and a Mean of height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group III j (N =1)	50	35.65 ± 0.26	168.23 ± 2.3
Group III k (N =1)	55	35.65 ± 0.27	168.23 ± 2.4
Group III l (N =1)	60	35.65 ± 0.25	168.23 ± 2.5

Group III D determines the mean of control subjects with age between 50-60 years,mean BMI 35.65 and a mean height of 168.23.Group III j(control subject with age 50 years with BMI 35.6 ± 0.26),GroupIII k (control subject with age 55 years with BMI 35.6 ± 0.27),Group III l (control subject with age 60 years with BMI 35.6 ± 0.25).

Group IV D (Mean of Hypertensive subjects with age between 50-60 Mean BMI 35.65 and a Mean of height of 168.23)			
Grouping	**Age**	**BMI**	**Height**
Group IV j (N =3)	50	35.65 ± 0.26	168.23 ± 2.3
Group IV k (N =3)	55	35.65 ± 0.27	168.23 ± 2.4
Group IV l (N =6)	60	35.65 ± 0.25	168.23 ± 2.5

Group IV D determines the mean of Hypertensive subjects with age between 50-60 years ,mean BMI 35.65 and mean height of 168.23.Group IV j(Hypertensive subjects with age 50 years with BMI 35.65± 0.26),GroupIV k(Hypertensive subject

with age 55 years with BMI 35.65± 0.27),Group IV l(Hypertensive subject with age 60 years with BMI 35.65± 0.25),N= Number of patients in each group.

6.6 Inclusion Criteria

i) Hypertension with SBP- 140-159 mm Hg, DBP- 90-99 mm of Hg with >10 years duration

ii) Age between 30-60 years

iii) Body mass index 18- 36

6.7 Exclusion criteria

1. History of Diabetes.
2. History of peripheral vascular disease.
3. Pregnancy.
4. Alcohol abuse, Smoking, Tobacco users.
5. Terminally ill hypertensive patients.
6. History of Leprosy.
7. Patients on other drugs which will impair/affect nerve conduction parameters like anticancer drugs, colchicine, ethambutol, lithium, phenytoin, isoniazid, leflunomide, dapsone, chloroquine, amiodarone etc.

8. Carpal tunnel syndrome
9. End stage renal failure
10. Stroke.
11. Any medical disorders which impairs/affects nerve conduction parameters.
12. Patients with h/o exposure to environmental toxins like lead, mercury, arsenic, thalium etc.

6.8 Parameters:

Nerve conduction parameters like

1. Duration,Latency(msec),conduction velocity (mtsec),amplitude (mv) of motor peroneal nerve.
2. Duration,Latency(msec),conduction velocity(mtsec),amplitide (mv) of motor tibial nerve.
3. Duration,Latency(msec), conduction velocity(mtsec),amplitude(mv) of sensory sural nerve.
4. Duration,Latency(msec),conduction velocity(mtsec), amplitude (mv) of sensory superficial peroneal nerve.

6.9 Instrument used:

The instrument used for this study was computerized RMS ALERON 401 EMG/NCV/EP system designed for any neurophysiologic application.This machine includes nerve conduction study,needle electromyography(EMG), F Wave,H reflex and all evoked potentials.This was supplied by Recorders and Medicare system Pvt. Ltd.Chandigrah,India.

6.10 Institutional Ethical Committee (IHEC) Approval:

The study proposal was submitted to Institutional Human Ethical Committee(IHEC) of SreeMookambika Institute of Medical sciences (SMIMS) Kulasekharam (K.K.District),Tamilnadu for approval and the research proposal was approved by the Institutional Human Ethics committee(IHEC) of SMIMS with Ref. no. SMIMS/IHEC/2013/A/14.The certificate of approval for the same has been enclosed in annexure.

6.11 Procedure

6.11.1 Establishment of BMI:

Volunteers's height will be measured in barefoot to the nearest fraction of 0.1cm by using wall fixed stadiometer. Body weight will be recorded to the nearest fraction of 0.1 kg by using a portable weighing machine. Subjects will be asked to

take off his/her shoes and jackets before weighing. Body Mass Index is calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2) using standard protocol.

6.11.2 Establishment of Blood Pressure status:

All control volunteers and hypertensive patients underwent blood pressure measurements.Standard mercury sphygmomanometer with appropriate cuff size was used to measure blood pressure. The subject was asked to sit relaxed in a chair with her/his arm supported comfortably and the pressure cuff was applied closely to the upper arm. The cuff was rapidly inflated to pressure above the level at which the radial pulse could no longer be felt. The stethoscope was placed lightly over the brachial artery and the mercury column was immediately allowed to fall at the rate of 2 mmHg per second. The first perception of the sound was taken as the systolic pressure and then the mercury was allowed to fall further till the sound ceased to be tapping in quality, became fully muffled, and finally disappeared. The level where it disappeared was taken as the diastolic pressure. The cuff was then deflated to zero pressure. The measurement was repeated twice with five-minute interval and the average taken for accuracy.

6.11.3 Nerve conduction study evaluation:

All subjects were investigated by a electrophysiological study of the motor tibial nerve, motor common peroneal nerve, sensory superficial peroneal nerve, sensory sural nerve on both limbs by the RMS-EMG machine.

All subjects were lying comfortably in supine position on an examination couch with the upper limb abducted 10-15^0 and flexed 10^0-15^0 at the elbow joint.

6.11.4 MotorTibial nerve conduction procedure:

Recording electrode/active electrode is placed on abductor hallicis or abductor digitiquinti,slightly below and anterior to navicular tuberosity.Reference electrode is placed distally to active electrode over the muscle tendon near the metatarsal head.Ground electrode is placed between the recording electrode and stimulation site (S1).

Stimulation is given on both sites such as distal site and proximal site.The distal site stimulation is given behind and proximal to the medial malleolus (S1) as shown in Figure 6.

Figure 6: Pictorial representation of tibial nerve conduction study: Distal nerve stimulation.

The proximal stimulation is given in the popliteal fossa,alongthe flexor crease of the knee (S2), slightly lateral to midline in popliteal fossa as shown in Figure 6.

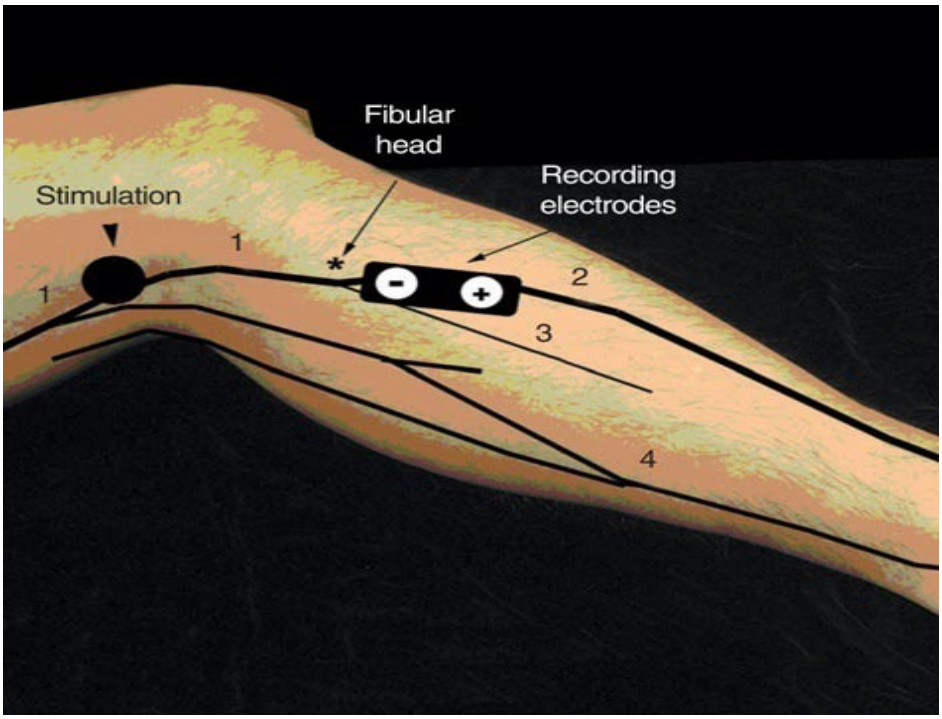
From the stimulation sites,CMAPduration,latency,amplitude and conduction velocity are determined in the motor tibial nerve.

Figure 7: Pictorial representation of tibial nerve conduction study: Proximal nerve stimulation.

6.11.5 Motor common peroneal nerve conduction procedure:

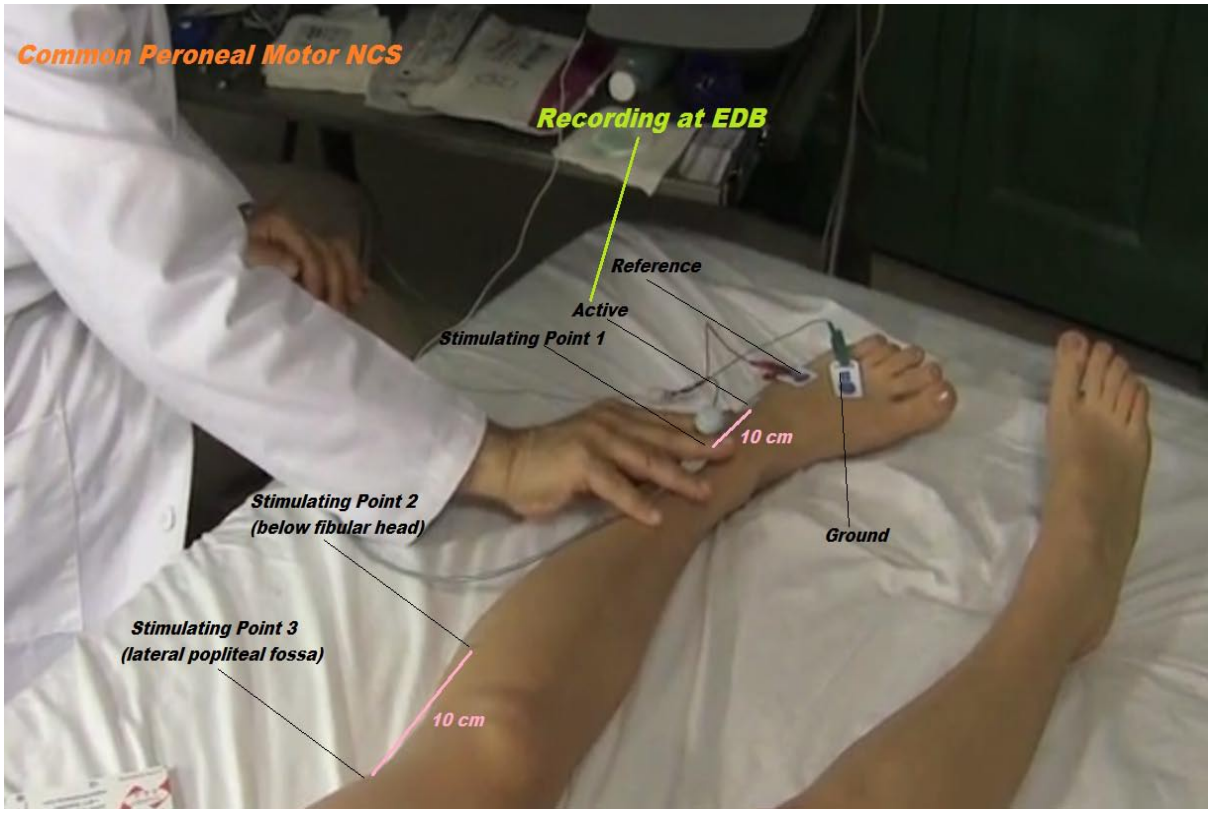
Recording electrode /active electrode is placed on extensor digitorumbrevis.Reference electrode is placed distal to the active electrode over the muscle tendon.Ground electrode is placed between recording electrode and stimulation site.

Figure 8: Placement of electrodes and stimulation site for common peroneal nerve conduction study.



Stimulation is given at ankle; 2cm distal to fibular neck, at the neck of fibula and 5-8 cm above the fibular neck for motor common peroneal nerve conduction study as shown in Figure 8 & 9.CMAP duration,amplitude,latency and conduction velocity are determined.

Figure 9: Pictorial representation of common peroneal nerve conduction study.

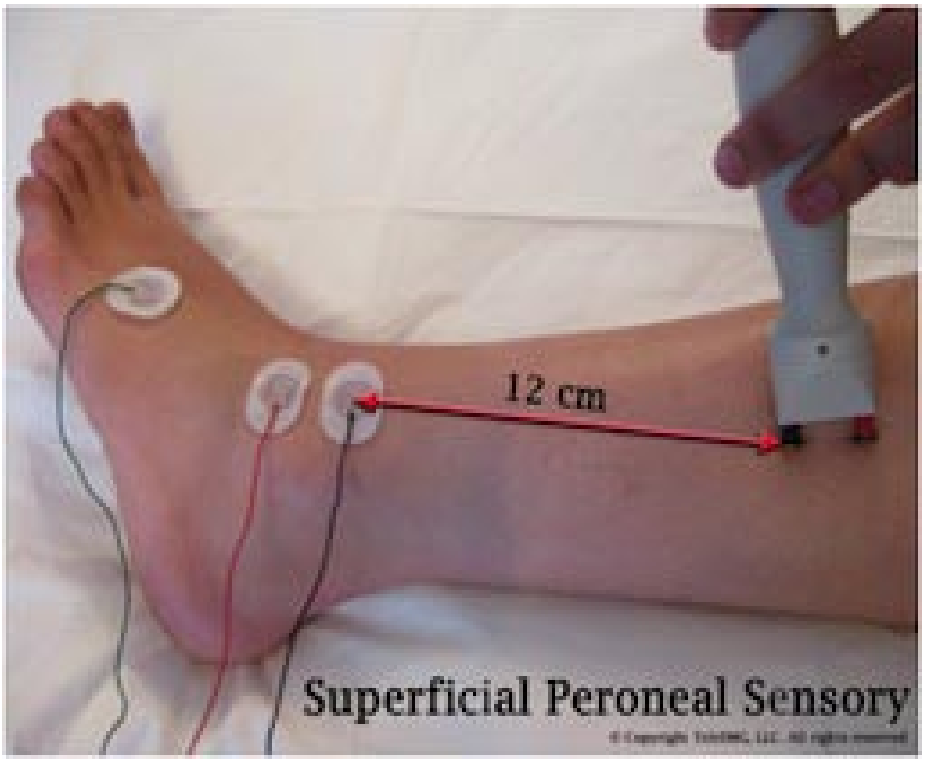


6.11.6 Sensory superficial peroneal nerve conduction procedure:

Recording electrode /active electrode is placed just above the junction of lateral third of a line connecting the malleoli.Reference electrode is placed 3cm

distally to the active electrode.Ground electrode is placed between the recording electrode and stimulation site.

Figure 10: Pictorial representation of sensory superficial peroneal nerve conduction study.



Stimulation is given 10-15 cm proximal to upper edge of lateral malleolus anterior to peroneouslongus for sensory superficial peroneal nerve conduction study as shown in Figure 10.SNAP duration,amplitude, latency and conduction velocity are determined.

6.11.7 Sensorysural nerve conduction procedure:

Recording electrode /active electrode is placed between lateral malleolus and tendoachilles.Ground electrode is placed between the recording electrode and stimulation site.

Figure 11: Pictorial representation of sensory sural nerve conduction study.

Stimulation is done antidromically 10-16 cm proximal to recording electrode distal to lower border of gastronemius at the junction of middle and lower third of leg as shown in Figure 11

6.12 Statistical methods of analysis

The data was entered into the Microsoft Office Excel 2007 for windows.GraphpadInstat version 3.06,32bit for windows was used to analyze the data.One way ANOVA followed by Bonferroni's post hoc test was used to find the statistical significance between the groups. $P<0.05$ was considered as statistically significant.

7. Results

7.1 Study subjects:

In this study, total of 136 subjects volunteered after considering the inclusion and exclusion criteria. They were divided into two groups which include, 28 control subjects and 108 hypertensive patients. This grouping was further subdivided based on mean BMI and age.The study was conducted with a mean height obtained from a range of heights of the study subjects. The baseline data with BMI calculation is given in Table 8.

Table 8 : Basic data and BMI of Control and Hypertensive subjects for the age range of 30-60 years

Age group (years)	**Mean Height (cm)**	**Mean Body weight (kg)**	**Mean BMI (m^2/kg)**
30-60	168.23 ± 2.3	48.73 ± 1.8	19.5 ± 0.26
30-60	168.23 ± 2.3	70.46 ± 2.5	26.75 ± 0.27
30-60	168.23 ± 2.3	83.00 ± 3.6	31.5 ± 0.25
30-60	168.23 ± 2.3	83.93 ± 4.2	35.65 ± 0.26

Total no of subjects utilized for the basic data assessment N = 136 subjects

7.2 Blood Pressure Measurements

Table 9a and 9b represents blood pressure measurements among the control and hypertensive subjects with varying mean BMI and age.

The blood pressure changes among the study groups were statistically compared and the results are as follows.

In the control subjects presented in table 8a and 8b; BMI and age did not show statistical significant changes in blood pressure measurements in the age group of 30-45 years. However, blood pressure measurements showed slightly significant changes to the statistical level of $p<0.01$ in Group III C (BMI 31.5, age 50-60 years) and peak statistical significance of $p< 0.001$ in Group III D (BMI 35.65, age 50-60 years).

In the hypertensive subjects as presented table 8a and 8b, BMI and Age showed statistically significant increase in blood pressure in Group II B (BMI 26.75, age 30-45 years)($p<0.001$). This statistical significance remained at $p<0.001$ in all other BMI groups in the age range 30-45 and 50-60 years ; Group II C (BMI 31.5, age 30-45 yrs), Group II D (BMI 35.65, age 30-45 yrs), Group IV A (BMI 19.5, age 50-60 yrs), Group IV B (BMI 26.75, age 50-60 yrs), Group IV C (BMI 31.5, age 50-60 yrs), Group IV D (BMI 35.65, age 50-60 yrs).

Table 9a: Blood Pressure measurements among control and hypertensivesin Age 30-45 years with Mean BMI and Mean Height

Grouping	Systolic BP	Diastolic BP
Group I A	122.05 ± 0.06	80.38 ± 0.7
Group II A	122.14 ± 0.01 a*	82.06 ± 0.22 a*
Group I B	122.07 ± 0.05 b^{NS}	80.48 ± 0.55 b^{NS}
Group II B	124.00 ± 0.01 c***d***	84.08 ± 0.2 c***d***
Group I C	122.09 ± 0.06 e^{NS}	80.53 ± 0.54 e^{NS}
Group II C	126.19 ± 0.01 f***g***	86.09 ± 0.22 f***g***
Group I D	122.10 ± 0.04 h^{NS}	80.68 ± 0.46 h^{NS}
Group II D	128.24 ± 0.01 i***j***	88.09 ± 0.22 i***j***

a = Group I A vs Group II A (BMI 19.5, age 30-45 yrs)

b = Group I A vs Group I B (Grp I A- BMI 19.5, Grp I B- BMI 26.75, age 30-45 yrs)

c = Group I B vs Group II B (BMI 26.75, age 30-45 yrs)

d = Group II A vs Group II B (Grp II A- BMI 19.5, Grp II B- BMI 26.75, age 30-45 yrs)

e = Group I A vs Group I C (Grp I A- BMI 19.5, Grp I C- BMI 31.5, age 30-45)

f = Group I C vs Group II C (BMI 31.5, age 30-45 yrs)

g = Group II A vs Group II C (Grp II A- BMI 19.5, Grp II C- BMI 31.5, age 30-45 yrs)

h = Group I A vs Group I D (Grp I A –BMI 19.5, Group I D-35.65, age 30-45 yrs)

i = Group I D vs Group II D (BMI 35.65**,** age 30-45 yrs)

j = Group II A vs Group II D (Grp II A –BMI 19.5, Group II D-35.65, age 30-45 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

Table 9b: Blood Pressure among control and hypertensives in Age 50-60 yrs with Mean BMI and Mean Height

Grouping	Systolic BP	Diastolic BP
Group III A	122.12 ± 0.05	80.5 ± 0.36
Group IV A	128.24 ± 0.01 a***	88.04 ± 0.25 a***
Group III B	122.13 ± 0.06 b^{NS}	80.60 ± 0.36 b^{NS}
Group IV B	130.24 ± 0.01 c***d***	90.18 ± 0.25 c***d***
Group III C	122.37 ± 0.06 e**	82.1 ± 0.36 e**
Group IV C	132.55 ± 0.01 f***g***	92.03 ± 0.25 f***g***
Group III D	122.4 ± 0.06 h***	82.20 ± 0.36 h***
Group IV D	134.56 ± 0.01 i***j***	98.03 ± 0.25 i***j***

a = Group III A vs Group IV A (BMI 19.5, age 50-60 yrs)

b = Group III A vs Group III B (Grp III A- BMI 19.5, Grp III B- BMI 26.75, age 50-60 yrs)

c = Group III B vs Group IV B (BMI 26.75, age 50-60 yrs)

d = Group IV A vs Group IV B (Grp IV A- BMI 19.5, Grp IV B- BMI 26.75, age50-60 yrs)

e = Group III A vs Group III C (Grp III A- BMI 19.5, Grp III C- BMI 31.5, age 50-60 yrs)

f = Group III C vs Group IV C (BMI 31.5, age 30-45 yrs)

g = Group IV A vs Group IV C (Grp IV A- BMI 19.5, Grp IV C- BMI 31.5, age 50-60 yrs)

h = Group III A vs Group III D (Grp III A –BMI 19.5, Group III D-35.65, age 50-60 yrs)

i = Group III D vs Group IV D (BMI 35.65, age 50-60 yrs)

j = Group IV A vs Group IV D (Grp IV A –BMI 19.5, Group IV D-35.65, age 50-60 yrs)

NS = Non significant, * = $p \leq 0.05$, ** = $p < 0.01$, *** = $p < 0.001$

7.3 Nerve Conduction Study

Nerve Conduction studies were conducted for the lower proximities. Table 9a and 9b represents the effect of BMI and age on tibial nerve conduction study variables in control and hypertensive subjects

7.3.1 MotorTibial Nerve conduction variables:

From the Table 10a and 10b CMAP latency and conduction velocities of tibial nerve in the control subjects starts to decrease significantly($p<0.05$) from a BMI of 31.5 and age 30-45 years(Group I C), and statistical significance is also decreased with $p<0.01$ at BMI 35.65 and age 30-45 years(Group I D). CMAP latency and conduction velocity attain a significant statistical peak decrease of $p<0.001$ with a BMI of 19.5 and age 50-60 years(Group III A).

This decreased statistical significance $p<0.001$ maintains with Increasing BMI and age of other Groups (Group III B (BMI 26.75), Group III C (BMI 31.5), Group III D (BMI 35.65), age 50-60 yrs.

CMAP duration and Amplitude of tibial nerve of control subjects attains statistical significant decrease ($p<0.05$) at a BMI 35.65 in the age 30-45 years (Group I D).However duration and amplitude showed significance of $p<0.01$ at a BMI of 31.5 and 35.65 in Group IIIC and IIID respectively in the age group of 50-

60 years.In Group IIID (BMI 35.65) showed statistical significance of $p<0.001$ in the age group of 50-60 years.

In the Hypertensive subjects, the onset of statistical peak significance ($p<0.001$) occurs in Group II D in BMI of 35.65 at a younger age range 30-45 yrs. Nerve conduction variables such as duration, amplitude, latency and conduction velocity attain peak statistical significance ($p<0.001$) at the same time in all other BMI groups of age 50-60 years.

Table 10a: Effect of hypertension on BMI on Motor Tibial Nerve conduction study variables in age group of 30-45 yrs

GROUPING	Motor Nerve	CMAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group I A	TIBIAL	6.40 ± 0.26	11.69 ± 0.5	10.18 ± 0.39	51.2 ± 0.15
Group II A	TIBIAL	6.34 ± 0.22 a^{NS}	11.56 + 0.16 a^{NS}	10.16 + 0.35 a^{NS}	50.6 + 0.15 a^{NS}
Group I B	TIBIAL	6.25 ± 0.26 b^{NS}	11.64 ± 0.15 b^{NS}	10.18 ± 0.39 b^{NS}	51.15 ± 0.16 b^{NS}
Group II B	TIBIAL	5.60 ± 0.39 c^{*}	11.59 ± 0.1 c^{NS}	9.56 ± 0.15 $c^{*}d^{*}$	44.17 ± 0.18 $c^{*}d^{***}$
Group I C	TIBIAL	6.13 ± 0.30 e^{NS}	11.56 ± 0.20 e^{NS}	9.73 ± 0.17 e^{*}	50.98 ± 0.17 e^{*}
Group II C	TIBIAL	5.73 ± 0.15 $f^{*}g^{**}$	11.39 ± 0.14 $f^{NS}g^{*}$	9.25 ± 0.25 $f^{**}g^{**}$	43.17 ± 0.18 $f^{***}g^{***}$
Group I D	TIBIAL	6.09 + 0.29 h^{*}	11.52 ± 0.13 h^{*}	9.59 ± 0.32 h^{*}	50.68 ± 0.17 h^{**}
Group II D	TIBIAL	4.62 ± 0.26 i***j***	10.00 ± 0.33 i***j***	6.67 ± 0.65 i***j***	40.86 ± 0.17 i***j***

a = Group I A vs Group II A (BMI 19.5, age 30-45 yrs),

b = Group I A vs Group I B (Grp I A- BMI 19.5, Grp I B- BMI 26.75, age 30-45 yrs)

c = Group I B vs Group II B (BMI 26.75, age 30-45 yrs)

d = Group II A vs Group II B (Grp II A- BMI 19.5, Grp II B- BMI 26.75, age 30-45 yrs)

e = Group I A vs Group I C (Grp I A- BMI 19.5, Grp I C- BMI 31.5, age 30-45)

f = Group I C vs Group II C (BMI 31.5, age 30-45 yrs)

g = Group II A vs Group II C (Grp II A- BMI 19.5, Grp II C- BMI 31.5, age 30-45 yrs)

h = Group I A vs Group I D (Grp I A –BMI 19.5, Group I D-35.65, age 30-45 yrs)

i = Group I D vs Group II D (BMI 35.65, age 30-45 yrs)

j = Group II A vs Group II D (Grp II A –BMI 19.5, Group II D-35.65, age 30-45 yrs)

NS = Non significant, * = p≤0.05, = p<0.01, *** = p<0.001**

Table 10b: Effect of hypertension on BMI on Motor Tibial Nerve conduction study variables in age group of 50-60 yrs

GROUPING	Motor Nerve	CMAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group III A	TIBIAL	6.01 ± 0.2	13.88 ± 0.15	9.68 ± 0.3	49.92 ± 0.3
Group IV A	TIBIAL	5.71 ± 0.15 a*	13.3 ± 0.13 a***	8.95 ± 0.4 a**	40.25 ± 0.13 a***
Group III B	TIBIAL	5.87 ± 0.25 b*	13.51 ± 0.11 b**	9.58 ± 0.36 b*	48.92 + 0.16 b***
Group IV B	TIBIAL	4.61 ± 0.4 c*d**	12.2 ± 0.14 c***d***	7.25 ± 0.25 c***d**	39.25 ± 0.14 c***d***
Group III C	TIBIAL	5.71 ± 0.2 e**	13.12 ± 0.10 e***	9.18 ± 0.24 e**	47.92 ± 0.08 e***
Group IV C	TIBIAL	4.11 ± 0.3 f***g***	11.7 ± 0.16 f***g***	6.75 ± 0.09 f***g***	38.25 ± 0.13 f***g***
Group III D	TIBIAL	5.61 ± 0.25 h***	12.82 ± 0.15 h***	8.68 ± 0.4 h**	46.92 ± 0.13 h***
Group IV D	TIBIAL	3.11 ± 0.2 i***j***	11.2 ± 0.14 i***j***	5.25 ± 0.3 i***j***	37.25 ± 0.13 i***j***

a = Group III A vs Group IV A (BMI 19.5, age 50-60 yrs)

b = Group III A vs Group III B (Grp III A- BMI 19.5, Grp III B- BMI 26.75, age 50-60 yrs)

c = Group III B vs Group IV B (BMI 26.75, age 50-60 yrs)

d = Group IV A vs Group IV B (Grp IV A- BMI 19.5, Grp IV B- BMI 26.75, age50-60 yrs)

e = Group III A vs Group III C (Grp III A- BMI 19.5, Grp III C- BMI 31.5, age 50-60 yrs)

f = Group III C vs Group IV C (BMI 31.5, age 30-45 yrs)

g = Group IV A vs Group IV C (Grp IV A- BMI 19.5, Grp IV C- BMI 31.5, age 50-60 yrs)

h = Group III A vs Group III D (Grp III A –BMI 19.5, Group III D-35.65, age 50-60 yrs)

i = Group III D vs Group IV D (BMI 35.65, age 50-60 yrs)

j = Group IV A vs Group IV D (Grp IV A –BMI 19.5, Group IV D-35.65, age 50-60 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

7.3.2 Motor Common Peroneal Nerve conduction variables:

Table 11a and 11b reflects the effects of BMI and age on common peroneal nerve conduction variables in control and hypertension subjects.

In control subjects, Nerve conduction parameters such as CMAP Duration, Amplitude, latency and conduction velocity attains statistical significant decrease of $p<0.1$ at a BMI of 31.5 (Group I C age 30-45 yrs). This significant decrease sustains itself in the other Groups also; Group I D (BMI 35.65, age 30-45 yrs), Group III A (BMI 19.5, age 50-60 yrs). Also there is a statistical significance of $p<0.01$ in Group III B (BMI 26.75, age 50-60 yrs), Group III C (BMI 31.5, age 50-60 yrs) Group III D (BMI 35.65, age 50-60 yrs)

In Hypertensive subjects CMAP duration, amplitude, latency and conduction velocity attained statistically significant decrease in Group II B (BMI 26.75, age 30-45 yrs) ($p<0.1$); CMAP duration, amplitude, latency and conduction velocity attains statistically significant peak decrease of $p<0.001$ in Group II D (BMI 35.65, age 30-45 years) and thereafter the statistical decrease maintained at the level of $p<0.001$ with increasing BMI and age groups, Group IV A (BMI 19.5, age 50-60 years), Group IV B (BMI 26.75,age 50-60 yrs), Group IV C (BMI 31.5, age 50-60 yrs), Group IV D (BMI 35.65, age 50-60 yrs)

Table 11a : Effect of hypertension on BMI on Motor Common Peroneal Nerve conduction study variables in age group of 30-45 yrs

GROUPING	Motor Nerve	CMAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group I A	Common Peroneal	6..66 ± 0.26	3.97 ± 0.15	9.72 ± 0.39	51.12 ± 0.31
Group II A	Common Peroneal	6.45 ± 0.24 a^{NS}	3.22 ± 0.03 a^{NS}	9.56 ± 0.37 a^{NS}	50.97 ± 0.31 a^{NS}
Group I B	Common Peroneal	6.46 ± 0.22 b^{NS}	3.74 ± 0.15 b*	9.48 ± 0.31 b^{NS}	50.87 ± 0.31 b^{NS}
Group II B	Common Peroneal	6.08 ± 0.17 c*d*	3.66 ± 0.22 c^{NS}d**	8.82 ± 0.32 c*d*	50.29 ± 0.26 c*d**
Group I C	Common Peroneal	6.23 ± 0.15 e*	3.50 ± 0.15 e**	9.01 ± 0.34 e*	50.72 ± 0.31 e*
Group II C	Common Peroneal	5.56 ± 0.26 f**g**	3.39 ± 0.15 f^{NS}g***	8.35 ± 0.17 f**g***	49.87 ± 0.13 f**g***
Group I D	Common Peroneal	6.20 ± 0.20 h*	3.48 ± 0.11 h**	8.99 ± 0.35 h*	50.69 ± 0.27 h*
Group II D	Common Peroneal	5.26 ± 0.24 i***j***	2.92 ± 0.10 i***j***	8.12 ± 0.17 i***j***	49.87 ± 0.13 i***j***

a = Group I A vs Group II A (BMI 19.5, age 30-45 yrs)

b = Group I A vs Group I B (Grp I A- BMI 19.5, Grp I B- BMI 26.75, age 30-45 yrs)

c = Group I B vs Group II B (BMI 26.75, age 30-45 yrs)

d = Group II A vs Group II B (Grp II A- BMI 19.5, Grp II B- BMI 26.75, age 30-45 yrs)

e = Group I A vs Group I C (Grp I A- BMI 19.5, Grp I C- BMI 31.5, age 30-45)

f = Group I C vs Group II C (BMI 31.5, age 30-45 yrs)

g = Group II A vs Group II C (Grp II A- BMI 19.5, Grp II C- BMI 31.5, age 30-45 yrs)

h = Group I A vs Group I D (Grp I A –BMI 19.5, Group I D-35.65, age 30-45 yrs)

i = Group I D vs Group II D (BMI 35.65, age 30-45 yrs)

j = Group II A vs Group II D (Grp II A –BMI 19.5, Group II D-35.65, age 30-45 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

Table 11b: Effect of hypertension on BMI on Motor Common Peroneal Nerve conduction study variables in age group of 50-60 yrs

GROUPING	Motor Nerve	CMAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group III A	Common peroneal	6.23 ± 0.15	3.36 ± 0.12	9.19 ± 0.3	50.33 ± 0.25
Group IV A	Common peroneal	5.80 ± 0.2 a*	2.83 ± 0.12 a**	7.87 ± 0.4 a**	48.38 ± 0.10 a***
Group III B	Common peroneal	6.08 ± 0.14 b*	3.21 ± 0.10 b**	7.62 ± 0.44 b**	49.47 ± 0.1 b**
Group IV B	Common peroneal	4.90 ± 0.25 c***d**	2.18 ± 0.13 c***d**	5.80 ± 0.20 c***d***	46.00 ± 0.50 c***d***
Group III C	Common peroneal	5.86 ± 0.10 e**	3.21 ± 0.12 e***	7.09 ± 0.45 e**	49.30 ± 0.35 e***
Group IV C	Common peroneal	4.71 ± 0.2 f***g***	2.06 ± 0.07 f***g***	3.88 ± 0.3 f***g***	44.92 ± 0.8 f***g***
Group III D	Common peroneal	5.56 ± 0.10 h**	3.06 ± 0.11 h***	7.88 ± 0.3 h**	48.47 ± 0.1 h***
Group IV D	Common peroneal	3.71 ± 0.2 i***j***	1.4 ± 0.14 i***j***	2.88 ± 0.4 i***j***	43.92 ± 0.7 i***j***

a = Group III A vs Group IV A (BMI 19.5, age 50-60 yrs)

b = Group III A vs Group III B (Grp III A- BMI 19.5, Grp III B- BMI 26.75, age 50-60 yrs)

c = Group III B vs Group IV B (BMI 26.75, age 50-60 yrs)

d = Group IV A vs Group IV B (Grp IV A- BMI 19.5, Grp IV B- BMI 26.75, age50-60 yrs)

e = Group III A vs Group III C (Grp III A- BMI 19.5, Grp III C- BMI 31.5, age 50-60 yrs)

f = Group III C vs Group IV C (BMI 31.5, age 30-45 yrs)

g = Group IV A vs Group IV C (Grp IV A- BMI 19.5, Grp IV C- BMI 31.5, age 50-60 yrs)

h = Group III A vs Group III D (Grp III A –BMI 19.5, Group III D-35.65, age 50-60 yrs)

i = Group III D vs Group IV D (BMI 35.65, age 50-60 yrs)

j = Group IV A vs Group IV D (Grp IV A –BMI 19.5, Group IV D-35.65, age 50-60 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

7.3.3 Sensory Superficial Peroneal Nerve conduction variables

Table 12a and 12 b represents the effect of BMI and age on sensory superficial peronealnerve in the control and hypertensive subjects.

In control subjects SNAP duration, amplitude, latency and conduction velocity attains a statistical significant decrease of $p<0.01$ at a BMI of 31.5 in the age group of 30-45 years (Group I C). This significance of $p<0.01$ is sustained at a BMI of 35.65 in the age group of 30-45 years.(Group ID).The statistical significance reaches peak decrease of $p<0.001$ in the Group III B (BMI 26.75, age 50-60 yrs) which, is sustained in the other groups, Group III C (BMI 31.5, age 50-60 yrs), Group III D (BMI 35.65 age 50-60 years).

In the hypertensive group, SNAP duration, amplitude, latency, conduction velocity attained statistical significant decrease of $p<0.01$ at a lower BMI of 26.75 in the age group of 30-45yrs (Group II B).This is in contrast to the control subjects where significant changes occur in a later BMI (Group I C). The statistical significance reaches peak decrease of $p<0.001$ at BMI 31.5 and BMI 35.65 in the age of 30-45 years.The statistical significance also reaches peak decrease of $p<0.001$ at a BMI of 26.75 (Group III B), 31.5(Group III C), 35.65 (Group III D) in the age group of 50-60 years.

Table 12a: Effect of hypertension on BMI on Sensory Superficial Peroneal Nerve conduction study variables in age group of 30-45 yrs

GROUPING	Sensory Nerve	SNAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group I A	Superficial Peroneal	0.289 ± 0.001	13.03 ± 0.095	10.97 ± 0.096	49.03 ± 0.10
Group II A	Superficial Peroneal	0.288 ± 0.002 a^{NS}	12.93 ± 0.094 a^{NS}	10.89 ± 0.093 a^{NS}	48.99 ± 0.090 a^{NS}
Group I B	Superficial Peroneal	0.288 ± 0.001 b^{NS}	12.94 ± 0.095 b^{NS}	10.93 ± 0.095 b^{NS}	48.97 ± 0.095 b^{NS}
Group II B	Superficial Peroneal	0.280 ± 0.002 c**d**	12.63 ± 0.095 c**d**	10.68 ± 0.095 c**d**	48.625 ± 0.098 c**d***
Group I C	Superficial Peroneal	0.283 ± 0.001 e**	12.73 ± 0.096 e**	10.675 ± 0.094 e**	48.73 ± 0.096 e**
Group II C	Superficial Peroneal	0.239 ± 0.002 f***g***	11.73 ± 0.096 f***g***	9.58 ± 0.093 f***g***	47.7 ± 0.094 f***g***
Group I D	Superficial Peroneal	0.282 ± 0.001 h**	12.66 ± 0.094 h**	10.65 ± 0.094 h**	48.68 ± 0.08 h**
Group II D	Superficial Peroneal	0.209 ± 0.002 i***j***	11.62 ± 0.095 i***j***	9.53 ± 0.093 i***j***	47.675 ±0.095 i***j***

a = Group I A vs Group II A (BMI 19.5, age 30-45 yrs)

b = Group I A vs Group I B (Grp I A- BMI 19.5, Grp I B- BMI 26.75, age 30-45 yrs)

c = Group I B vs Group II B (BMI 26.75, age 30-45 yrs)

d = Group II A vs Group II B (Grp II A- BMI 19.5, Grp II B- BMI 26.75, age 30-45 yrs)

e = Group I A vs Group I C (Grp I A- BMI 19.5, Grp I C- BMI 31.5, age 30-45)

f = Group I C vs Group II C (BMI 31.5, age 30-45 yrs)

g = Group II A vs Group II C (Grp II A- BMI 19.5, Grp II C- BMI 31.5, age 30-45 yrs)

h = Group I A vs Group I D (Grp I A –BMI 19.5, Group I D-35.65, age 30-45 yrs)

i = Group I D vs Group II D (BMI 35.65, age 30-45 yrs)

j = Group II A vs Group II D (Grp II A –BMI 19.5, Group II D-35.65, age 30-45 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

Table 12b : Effect of hypertension on BMI on Sensory superficial Peroneal Nerve conduction study variables in age group of 50-60 yrs

GROUPING	Sensory Nerve	SNAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group III A	Superficial peroneal	0.28 ± 0.002	12.64 ± 0.1	10.6 ± 0.1	48.64 ± 0.1
Group IV A	Superficial peroneal	0.198 ± 0.002 a***	11.6 ± 0.1 a***	9.44 ± 0.1 a***	47.74 ± 0.3 a***
Group III B	Superficial peroneal	0.25 ± 0.002 b***	12.03 ± 0.1 b***	9.7 ± 0.1 b***	48.00 ± 0.2 b***
Group IV B	Superficial peroneal	0.09 ± 0.002 c***d***	10.00 ± 0.1 c***d***	8.5 ± 0.1 c***d***	47.00 ± 0.1 c***d***
Group III C	Superficial peroneal	0.23 ± 0.001 e***	11.8 ± 0.09 e***	9.8 ± 0.08 e***	47.8 ± 0.2 e***
Group IV C	Superficial peroneal	0.08 ± 0.002 f***g***	9.00 ± 0.08 f***g***	8.00 ± 0.09 f***g***	46.00 ± 0.3 f***g***
Group III D	Superficial peroneal	0.22 ± 0.001 h***	11.7 ± 0.2 h***	9.7 ± 0.2 h***	47.7 ± 0.1 h***
Group IV D	Superficial peroneal	0.06 ± 0.002 i***j***	7.00 ± 0.1 i***j***	6.00 ± 0.1 i***j***	44.00 ± 0.3 i***j***

a = Group III A vs Group IV A (BMI 19.5, age 50-60 yrs)

b = Group III A vs Group III B (Grp III A- BMI 19.5, Grp III B- BMI 26.75, age 50-60 yrs)

c = Group III B vs Group IV B (BMI 26.75, age 50-60 yrs)

d = Group IV A vs Group IV B (Grp IV A- BMI 19.5, Grp IV B- BMI 26.75, age50-60 yrs)

e = Group III A vs Group III C (Grp III A- BMI 19.5, Grp III C- BMI 31.5, age 50-60 yrs)

f = Group III C vs Group IV C (BMI 31.5, age 30-45 yrs)

g = Group IV A vs Group IV C (Grp IV A- BMI 19.5, Grp IV C- BMI 31.5, age 50-60 yrs)

h = Group III A vs Group III D (Grp III A –BMI 19.5, Group III D-35.65, age 50-60 yrs)

i = Group III D vs Group IV D (BMI 35.65, age 50-60 yrs)

j = Group IV A vs Group IV D (Grp IV A –BMI 19.5, Group IV D-35.65, age 50-60 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

7.3.4 Sensorysural nerve conduction variables.

Table 13a and 13b represents the effect of BMI and age on sensory sural nerve in the control and hypertensive subjects.

In the control subjects, SNAPduration, amplitude, latency and conduction velocity of sural nerve attains statistical significance $p<0.001$ in Group I C (BMI 31.5, age 30-45 yrs) and this significance is sustained at a BMI of 35.65 in the age group of 30-45 years. This statistical significance is maintained with BMI 19.5(Group III A), 26.75(Group III B),31.5(Group III C),36.5(Group III D) in the age group 50-60 years.

In the hypertensive subjects amplitude and latency attained statistical significance of $p<0.01$ and duration as well as conduction velocity attained peak statistical significance in Group II B (BMI 26.75, age 30-45 years).However, SNAP duration, amplitude, conduction velocity attained peak statistical significance with $p<0.001$ in Group II C (BMI 31.5),Group II D(BMI 35.6) in age group 30-45 years and with BMI 19.5(Group IV A), 26.5(Group IV B), 31.5(Group IV C), 35.6(Group IV D) with age group 50-60 years.

Table 13a : Effect of hypertension on BMI on Sensory Sural Nerve conduction study variables in age group of 30-45 yrs

GROUPING	Sensory Nerve	SNAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group I A	Sural	0.539 ± 0.0009	15.77 ± 0.086	14.79 ± 0.087	33.29 ± 0.13
Group II A	Sural	0.538 ± 0.0008 a^{NS}	15.72 ± 0.085 a^{NS}	14.74 ± 0.086 a^{NS}	33.19 ± 0.12 a^{NS}
Group I B	Sural	0.538 ± 0.0006 b^{NS}	15.71 ± 0.084 b^{NS}	14.69 ± 0.083 b^{*}	33.19 ± 0.13 b^{NS}
Group II B	Sural	0.553 ± 0.0004 c***d**	15.47 ± 0.083 c**d**	14.47 ± 0.084 c**d**	32.86 ± 0.14 c***d***
Group I C	Sural	0.535 ± 0.007 e***	15.27 ± 0.086 e***	14.59 ± 0.083 e***	33.09 ± 0.13 e***
Group II C	Sural	0.0529 ± 0.0005 f***g***	14.87 ± 0.084 f***g***	13.89 ± 0.084 f***g***	32.69 ± 0.12 f***g***
Group I D	Sural	0.531 ± 0.0008 h***	14.97 ± 0.082 h***	14.29 ± 0.086 h***	31.99 ± 0.13 h***
Group II D	Sural	0.519 ± 0.007 i***j***	14.57 ± 0.085 i***j***	13.79 ± 0.085 i***j***	31.39 ± 0.11 i***j***

a = Group I A vs Group II A (BMI 19.5, age 30-45 yrs)

b = Group I A vs Group I B (Grp I A- BMI 19.5, Grp I B- BMI 26.75, age 30-45 yrs)

c = Group I B vs Group II B (BMI 26.75, age 30-45 yrs)

d = Group II A vs Group II B (Grp II A- BMI 19.5, Grp II B- BMI 26.75, age 30-45 yrs)

e = Group I A vs Group I C (Grp I A- BMI 19.5, Grp I C- BMI 31.5, age 30-45)

f = Group I C vs Group II C (BMI 31.5, age 30-45 yrs)

g = Group II A vs Group II C (Grp II A- BMI 19.5, Grp II C- BMI 31.5, age 30-45 yrs)

h = Group I A vs Group I D (Grp I A –BMI 19.5, Group I D-35.65, age 30-45 yrs)

i = Group I D vs Group II D (BMI 31.5, age 30-45 yrs)

j = Group II A vs Group II D (Grp II A –BMI 19.5, Group II D-35.65, age 30-45 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

Table 13b : Effect of hypertension on BMI on Sensory Sural Nerve conduction study variables in age group of 50-60 yrs

GROUPING	Sensory Nerve	SNAP			Conduction Velocity
		Duration	Amplitude	Latency	
Group III A	Sural	0.53 ± 0.0009	14.6 ± 0.09	13.87 ± 0.09	31.84 ± 0.10
Group IV A	Sural	0.50 ± 0.0007 a***	14.00 ± 0.09 a***	13.17 ± 0.09 a***	30.84 ± 0.10 a***
Group III B	Sural	0.51 ± 0.0008 b***	13.8 ± 0.09 b***	12.38 ± 0.09 b***	31.14 ± 0.09 b***
Group IV B	Sural	0.48 ± 0.0009 c***d***	12.8 ± 0.09 c***d***	12.27 ± 0.09 c***d***	30.64 ± 0.10 c***d***
Group III C	Sural	0.492 ± 0.0009 e***	13.3 ± 0.07 e***	11.87 ± 0.07 e***	30.54 ± 0.08 e***
Group IV C	Sural	0.46 ± 0.0009 f***g***	11.8 ± 0.09 f***g***	11.77 ± 0.06 f***g***	29.34 ± 0.1 f***g***
Group III D	Sural	0.47 ± 0.0008 h***	12.8 ± 0.09 h***	11.57 ± 0.05 h***	30.14 ± 0.1 h***
Group IV D	Sural	0.44 ± 0.0008 i***j***	10.8 ± 0.08 i***j***	10.77 ± 0.09 i***j***	28.34 ± 0.2 i***j***

a = Group III A vs Group IV A (BMI 19.5, age 50-60 yrs)

b = Group III A vs Group III B (Grp III A- BMI 19.5, Grp III B- BMI 26.75, age 50-60 yrs)

c = Group III B vs Group IV B (BMI 26.75, age 50-60 yrs)

d = Group IV A vs Group IV B (Grp IV A- BMI 19.5, Grp IV B- BMI 26.75, age50-60 yrs)

e = Group III A vs Group III C (Grp III A- BMI 19.5, Grp III C- BMI 31.5, age 50-60 yrs)

f = Group III C vs Group IV C (BMI 31.5, age 30-45 yrs)

g = Group IV A vs Group IV C (Grp IV A- BMI 19.5, Grp IV C- BMI 31.5, age 50-60 yrs)

h = Group III A vs Group III D (Grp III A –BMI 19.5, Group III D-35.65, age 50-60 yrs)

i = Group III D vs Group IV D (BMI 35.65, age 50-60 yrs)

j = Group IV A vs Group IV D (Grp IV A –BMI 19.5, Group IV D-35.65, age 50-60 yrs)

NS = Non significant, * = p≤0.05, ** = p<0.01, *** = p<0.001

8. Discussion

The present study was done to assess the effect of hypertension on increasing BMI and age in nerve conduction study variables in patients attending the outpatient Department of General Medicine.The clinical procedures were conducted at the research laboratory in the Department of Physiology at SreeMookambika Institute of Medical Sciences located at Kulasekaram, Kanyakumari district. This study was designed to assess the effect of hypertension on BMI and age on nerve conduction variables since there are very few studies done to correlate hypertension with peripheral neuropathy, with age and BMI as aggravating factors. In India hypertension is the third leading killer under category of non-communicable disease.[21]

8.1 BMI and Age:

136 participants of the study were categorized into two main groups Control group and hypertensive group.This grouping was further subdivided into various groups based on BMI and age. Table 7 represents mean calculation of height and BMI in various age groups.Case History was recorded for all the 136 participants to verify the inclusion and exclusion criteria.The basic data such as height and weight were recorded from which the BMI was calculated. Mean Height and Mean BMI were standardized. One

single mean height was chosen for the entire study for all the group subdivisions.

Mean BMI was divided into four major BMI's falling in the normal range 19.5, Pre-obese 26.75,Obese Class I 31.5, Obese class II 36.5.This was achieved by following the classification of world health organization.[116] The age grouping was subdivided into two ranges 30-45 yrs covering the younger subjects, and 50-60 yrs covering the elderly subjects.

8.2 Blood Pressure:

Table 9a and 9b represents the blood pressure measurements in the age range 30-45 yrs and 50-60 yrs, mean BMI in both control subjects and hypertensive patients. In the control subjects there was significant statistical increase in the levels only in the age range of 50-60 yrs in the obese class I (Group III C), and Obese Class II (Group III D).

This is in contrast with the hypertension subjects where significant changes in blood pressure occurs in the normal range BMI of 19.5 in age 30-45 yrs and the statistical peak significance occurs in Class II Obese (Group II D) in the range of 30-45 yrs.

8.3 Nerve conduction studies:

To assess the effect of hypertension on nerve conduction study variables along with BMI and age as co-factors; two motor nerves (Tibial and Common peroneal nerve) and two sensory nerves (Superficial peroneal and sural nerve) were studied in the control and hypertensive subjects.

Table 10a and 10b represents the variables of Tibial nerve conduction studies such as duration,latency,conduction velocity. Here the onset of statistical peak significance appears to occur in the Obese class I (Group III C) in the age range of 50-60 yrs.

Whereas,amplitude showed statistical significance which reaches the peak value in the control subjects only in the Group III D (Obese Class I) in the age range of 50-60 yrs.

These values are significant in contrast with the hypertension group in which changes in duration,Latency and conduction velocity appear to show peak statistical significance in the Obese Class II (Group II D) in the age range of 30-45 years. This is an earlier onset,when compared to the control subjects.

The amplitude changes also appear to occur in an earlier age range of 30-45 years,in the hypertensive subjects occurring in Group III D (Obese Class II).

Table 11 a and 11 b represent the nerve conduction variables occurring in the motor common peroneal nerve. The statistical trend of the motor common peroneal nerve conduction variables were similar and identical to the statistical trend of the motor tibial nerve, in which the onset of changes in nerve conduction study variables occurred at a later age (50-60 years) in the control group. The duration,latency and conduction velocity shows peak statistical significance in the above said age range in obese class I (Group III C). Whereas, the amplitude changes occur only in the obese class II (Group III D).

In the hypertensive subjects changes in duration,amplitude,latency and conduction velocity occur relatively at a younger age range of 30-45 yrs; obese class II (Group II D).

Table 12a and 12b represent the nerve conduction variables of sensory superficial peroneal nerve. The trend of statistical significance is similar when compared to the motor nerves in which changes occur in later age range (50-

60 years) in control group; whereas; in an earlier age in the hypertensive group (30-45 years).

Duration, amplitude, latency and conduction velocity showed statistical significance in Pre-obese state in the age range of 50-60 yrs (Group III C) in the control subjects.

Whereas, in Hypertension subjects, changes are observed in the obese class II (35.65) in the age range 30-45 years (Group II D).

Table 13a and 13b represent the nerve conduction variables of sensory sural nerve. Statistical significant changes in the sensory sural nerve occurred in the age range of 30-45 years,but the onset BMI was different in control and hypertensive subjects.

The BMI was obese class II (35.65) in control subjects (Group I D); whereas, in the hypertensive's the BMI was in the Pre-Obese (26.75)(Group II D) with age 30-45 years. The significant changes appeared in all the nerve conduction variables such as duration, amplitude, latency and conduction velocity in both the groups.

Though certain papers report a negative association between hypertension and peripheral neuropathy[96,97]. Our study presents a positive

correlation between hypertension and peripheral neuropathy. However, there are studies that present a positive correlation between hypertension and nerve conduction studies by Dhafir. I El-Yassinet. al.[51] BMI and age related studies done by Awang et al[99] observed that with increasing BMI and age in control subjects there is slowing of nerve conduction velocity in median (both motor and sensory) nerve with increasing BMI and age.

Another study published in the Indian J. PhysiolPharmacol in 2012 by Pawar SM et al.[117] has also similar findings related to our study. They report prolongation of distal motor latency with increasing BMI. They also observed F-wave minimum velocity which was significantly prolonged in motor tibial nerve

Dhafir I. El- Yassin[51] has clinically proved a positive correlation between hypertension and nerve conduction velocity and reports that patients with hypertension present peripheral sensory neuropathy mainly of axonal type with demyelination as an secondary outcome only in the sural nerve.

In our study demyelination and axonal changes observed as alterations in the nerve conduction study variables such as CMAP or SNAP latency and amplitude changes in hypertension the changes occurring at a relatively earlier age range 30-45 years in the obese class I (BMI 26.75) in the control

subjects the changes in the same age range 30-45 years at a higher range. These results are in agreement with Dhafir I. El- Yassin's paper.[51]

8.4 Molecular Pathophysiology Pertaining To Nerve Conduction Variables

Though we have a clear understanding that BMI and age can cause deficits in nerve conduction variables in control subjects; the presence of hypertension in a subject along the with age and BMI as co-factors could aggravate the deficits in nerve conduction variables at an earlier age when compared to control subjects thus making them prone to present with peripheral neuropathy.

Though our study has not included much pathophysiology experiments we were interested in finding a basic working molecular pathophysiologic mechanism that would enlighten us on what is the process of BMI and age in reducing the nerve conduction variables.

We hypothesize that hypertension mediated dyslipidemia can cause oxidative stress that in turn imbalances Angiotensin II and vasodialator balance especially nitric oxide and endothelin-1. The process is continued as a feed forward mechanism since the antioxidant status is compromised due to

oxidative damage to the antioxidant enzymes and the presence of high volume of free radicals being the primary culprits of oxidative stress.

Depletion of Nitric oxide is an outcome of oxidative stress which mediates the production of peroxynitrite a biological reaction of nitric oxide with single oxygen (free radical). The formation of peroxynitrite and free radicals and depletion of antioxidants mediate the activation of aging mechanisms such as senescence and apoptosis that culminate into axonal degeneration observed as CMAP or SNAP amplitude decrease with prolongation of duration in control and hypertensive subjects that occurs at earlier stage in the hypertensive subjects. This is possibly due to onset of oxidative stress at an earlier stage and its non-depletion,despite various therapies targeted at hypertension.

Axonal degeneration or apoptosis of the nerve occurs as an outcome of oxidative stress mediated by Poly-ADP-ribose polymerase [PARP], an death enzyme present within the Axon.

Demyelination is an outcome of degeneration of myelin which is also achieved by oxidative stress implementing uncontrolled and irreversible lipid peroxidation causing the degradation of myelin which causes latency changes in the nerve conduction.

Finally the Na^+K^+ATPase at the nodes of Ranvier 0 also lose functionality due to deprivation of ATP that is an outcome of inefficient mitochondrial functioning during the onset of Axonal degeneration.

All these processes finally culminate into functionally defective nerve, incapable of firing; and is witnessed clinically as peripheral neuropathy in the peripheral nerves in hypertension.

Crowley SD [118] and Yasunari K et al[119] have proved clinically that oxidative stress is an outcome of chronic inflammation in hypertensive subjects. The onset of oxidative stress in hypertensive subjects depletes the levels of nitric oxide via the formation of peroxynitrite. This mechanism has been clinically proved by Moriel P et al[120].

Peroxynitrite mediated activation of PARP has been experimentally been proved in spontaneously hypertensive rats by Dereset al.[121]. The association of PARP activity mediating axonal degeneration has been experimentally proved in a rat model of multiple sclerosis by Penberty WT and Tsunoda I[122]; and the presence of axonal degeneration in hypertension has been proved experimentally in SHR rats by Sanada LS et al[123]. SHR rats are molecular mimics of essential hypertension and they serve as good

counterparts in working the mechanisms behind essential hypertension that cannot be done in human subjects.

Demyelination has also been proved both clinically as latency changes in control subjects by Awanget al[99], and experimentally by Sanada LS et al[123]

Our study clearly demonstrates, axonal degeneration as changes in CMAP or SNAP amplitude and prolongation in duration in control subjects with higher BMI and age; whereas, in the essential hypertensives changes occurred in lower age range with increasing BMI.

Demyelination was also observed as latency changes in our study following the same trend of onset in control and hypertensive subjects as indicated for axonal degeneration.

Our findings are supported by clinical studies of Henry C. et al[124], who has studied the effect of aging on sensory nerve conduction parameters and has presented that sensory nerve conduction velocity does change with aging.

Aging mechanisms have experimentally proved in hypertension by Kung CF et al[125]

Demyelination is observed as latency changes with increasing BMI and age which has been clinically proved by Awanget al[99] and experimentally it has been proved by Sanada LS et al[123]

9. Conclusion

Hypertension enhanced the effect of BMI and age included increased blood pressure and slowing of nerve conduction variables.

Increasing BMI and age caused increased blood pressure and nerve conduction variables in the control subjects.

These effects were significantly increased in the hypertension with increasing BMI and age. Since the onset age of these variables occurred at an younger age.

10.Summary

Sensation, pain, and voluntary movements are very essential. These are molecularly controlled by the peripheral nerves.

In the present scenario urbanization is surplusly increasing in the percentile of non-communicable diseases. Especially diseases such as diabetes, hypertension, Obesity are perceived to cause deterioration in the peripheral nerves. This deterioration in the peripheral nerves is enhanced by BMI and age. The extent of deterioration has been well demonstrated in diabetes due to the high prevalence of diabetic foot.

But peripheral neuropathy is perceived to appear in hypertension but is an area very less worked and persists with a conflict of interest with certain authors acknowledging that hypertension can cause peripheral neuropathy while others perceive that hypertension could not cause such changes.

So our study was aimed to analyze whether hypertension caused nerve conduction variables deterioration and whether this could be enhanced by BMI and age.

This was a comparative descriptive study conducted with 136 subjects who were grouped into Group (n=27) normal subjects and Group II (n=108).

Both the groups were subdivided based on age, 30-35 yrs constituted the younger age group and 50-60 yrs constituted the older age group. Both age groups were further divided based on the BMI into four classes following the NIH classification. Into Normal (19.5 BMI), Obese class I (26.75BMI), Obese Class II (31.5 BMI), Obese Class III (36.5 BMI).

Basic data such as height and weight age and sex were recorded and the case history was studied BMI was calculated and blood pressure was measured using sphygmomanometer and nerve conduction variables of the tibial nerve, motor common peroneal nerve, superficial peroneal nerve and sensory sural nerve was recorded using RMS-EMG instrument supplied from Recorders and Medicare system Pvt. Ltd.Chandigrah,India.

The results analyzed showed that with increasing BMI significant blood pressure changes were caused along with increasing age and hypertension significantly increased changes making the changes making the changes at an earlier age.

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SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

KULASEKHARAM-629161

DEPARTMENT OF PHYSIOLOGY

CASE RECORD FORM

Study Title : Effect of hypertension on nerve conduction parameters in patients attending Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Serial No: **Date :**

Name :

Age:

Sex :

Address:

Occupation :

Contact No:

Hospital Reference No:

History of Hypertension:

Any other relevant history/ information:

General examination:

Height in (cm) :

Weight in (kg) :

BMI (Body mass index) :

Heart rate (per minute) :

BP (mm of Hg):

Systemic Examination:

Examination of central nervous system:

a)Examination of higher functions:

b)Examination of sensory system:

c)Examination of motor system:

d)Examination of reflexes:

e)Examination of cranial nerves:

Examination of other systems:

Blood pressure Measurement:

Systolic Bp(mm of Hg):

Diastolic Bp(mm of Hg):

Electrophysiological Investigations:

Nerve	Latency(millisec)		Amplitude (millivolt)		Conduction velocity (mt sec)		Duration	
	Right	Left	Right	Left	Right	Left	Right	Left
Sural (sensory)								
Tibial (motor)								
Peroneal (sensory)								
Peroneal (motor)								

ABBREVATIONS

AGE	Advanced Glycation End products
ANOVA	Analysis of Variance
BMI	Body Mass Index
CMAP	Compound MuscleAction Potential
CI	Confidence interval
DNA	Deoxyribo Nucleic Acid
EBF	Endothelial Blood Flow
HES	HydroxyethylStrachDeferoxamine
IGF	Insulin Growth Factor
JNC	Joint National Committee
LPO	Lipid Peroxidation
MDA	Malondialdehyde
NAP	Nerve Action Potential
NGF	Nerve Growth Factor
NT3	Neurotrophin- 3
NCS	Nerve Conduction Velocity
NBF	Nerve Blood Flow
NCV	Nerve Conduction Velocity
OR	Odds Ratio
PARP	Poly ADP Ribose Pathway
PNS	Peripheral Nervous System
PKC	Phosphokinase C
ROS	Reactive Oxygen Species
SDN	Strepotozotocin induced diabetic neuropathy
SHR	Spontaneously Hypertensive Rats
SNAP	Sensory Nerve Action Potential
TERT	Telomerase Reverse Transcriptase

CONSENT FORM

PART – I OF II

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear Volunteers,

We welcome you and thank you for your keen interest in participation in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. **Name of the principal Investigator :** **Dr. L. Aswathy**
   Post Graduate
   Dept of Physiology
   SMIMS, Kulasekharam.

2. **Name of the guide :** **Dr. M. S. Kumari Sheela (M.D)**
   Professor and Head
   Department of Physiology
   SMIMS, Kulasekharam.

3. **Name of the Co-guide :** **Dr. J. Kaniraj Peter (M.D)**
   Professor and Head
   Department of Medicine
   SMIMS, Kulasekharam.

4. **Institute :** Sree Mookambika Institute of Medical Sciences (SMIMS)
   Kulasekharam, Kanyakumari District, Tamilnadu.

5. **Title of the Study :**

Effect of Hypertension on Nerve conduction parameters in patients attending Sree Mookambika Institute of Medical Sciences,Kulasekharam.

6. Background Information:

The most important medical and public health issue and the single cause of death world wide is high blood pressure.The death occurs through heart attack, stroke and kidney disease.

The situation in India is graver, since with mordernization, we are trading healthy traditional diets for fatty foods, physical jobs for desk bound ones and calm rural life for stressful city life. India is slated to become the hypertension capital next to diabetic capital. There is also a rapid increase in the incidence and consequent prevalence of hypertension. So it is important to have a reliable information about the prevalence of Hypertension in different world regions for the development of national & International Health Policies for prevention and control of this condition.The increased risks are present in individuals ranging from 40- 89 years of age. Due to technological advances, there is dramatic change in life style of people and overall prevalence of Hypertension (JNL-VI) in South India is 12.5%.

In 95% of cases essential hypertension may precede the onset of diabetes.Hypertension is defined as sustained elevation of BP $\geq$ 140/90 mm of Hg. It is easy to diagnose, simple to treat and availability of drugs is present, but sometimes it remains undetected, untreated and sometimes treatment may not be adequately effective.

Nerve conduction study is an essential study in the diagnosis of peripheral neuropathies. It has become a reliable test in clinical settings for diagnosing diseases of peripheral nerves.

The constituent of electrophysiology and electrophysiological tests is nerve conduction or electroneurography. They are reliable and provide reproducible approaches to detection and characterization of nerve, muscle, neuromuscular junction diseases. Nerve conduction study consist of non invasive electrical stimulation of peripheral nerve at one site and non invasive measurement of evoked response at second site in the nerve (sensory or mixed nerve conduction) or over the muscle innervated by the nerve (motor nerve conduction)

Nerve conduction study measures duration,latency,amplitude and conduction velocity. Conduction velocity and latency denote the speed of nerve impulse propogation. They are altered in disease which cause demyelination. Amplitude denote the number of functioning fibres and it is altered in diseases causing axonal degeneration.

The world health theme according to WHO for the year 2013 is High blood pressure. The ultimate goal is to create greater awareness, healthy behaviour improved detection and enabling enviornment.

Inspite of thorough review it was found that several nerve conduction studies are done among normal individuals. There are very few studies across the world in nerve conduction study among hypertensives. Hence there is a need to look into these parameters particularly among rural population.

7. Aims and objectives:

1. To assess the effect of hypertension in nerve conduction Parameters.

2.To study the association of age and Body mass index on nerve conduction parameters in hypertensives.

8.. Scientific justification of the study:

Inspite of thorough review it was found that several nerve conduction studies are done among normal individuals. A study done on nerve conduction in healthy individual a premilinary age based study showed that age has definite effect on amplitude and duration of motor & sensory nerves. Another study done on body mass index on nerve conduction parameters showed that body mass index affect nerve conduction parameters.There are very few studies across the world in nerve conduction study among hypertensives. Hence there is a need to look into these parameters on hypertensives so that people can be made aware of the complications due to hypertension.

The world health theme according to WHO for the year 2013 is high blood pressure. The ultimate goal is to create greater awarness, healthy behaviour, improved detection and enabling environments.

9.Procedure of the study :

You are required to participate in this study only if you fully understand and agree to the requirements for the same. There will be no difference in the treatment you receive, nor will treatment be withheld based on your decision to participate in this study.

The study is conducted in collaboration with medicine department. By systematic random sampling 108 subjects with hypertension and 28 subjects without hypertension will be selected from the OPD of medicine department and BP will be measured by auscultatory method in sitting posture. Patients who will fall under my inclusion criteria with BP (SBP – 140-159 mm Hg, DBP – 90-99 mm Hg),age 30-60 years,BMI 18-36 will be recruited in this study after considering the exclusion criteria also. All subjects will undergo Nerve conduction tests in the research lab in department of physiology. Nerve conduction study will be done by RMS EMG Machine on tibial nerve, motor common peroneal nerve,sensory superficial nerve and sural nerve of both limbs in supine posture. Study volunteers will be explained thoroughly about the procedure and consent will be obtained from them before the study. Detailed history including age, sex, height, weight, BP will be recorded. The values will be noted and it is maintained in case record form. Nerve conduction study recorded from Nerve conduction measuring system is maintained in both Microsoft office excel as well as in hard copy.

10.Expected risks for the participant

Each electrical stimulation is very brief and the patient will feel a tingling sensation which may cause little discomfort.

11.Expected benefits of research for the participants :

The effect of Hypertension on Nerve conduction Parameters will be identified which will help in identifying the changes occurring in Peripheral Nerves due to Hypertension, so that the quality of life of the people will be maintained. It may be gratifying to know that your contributions is indispensable for the advancement of medical knowledge.

12. Maintenance of Confidentiality :

All your study records will be kept confidential. Your personal identity will not be revealed in any publication or release of results. Study records will be kept indefinitely for analysis and follow up.

13.Why have I been chosen to be in this study?

As u fall under my inclusion criteria you have been chosen.

14.How many people will be in the study? 128

15.Agreement of Compensation to the participants : NIL

16.Anticipated prorated payment,if ,any to the participant(s) of the study:

17.Can I withdraw from the study at any time during the study period?

Yes, you can withdraw from the study at any time during the study period.

18.If there is any new findings / information, would I be informed?

Yes, If there is any new findings / information, you will be informed.

19.Expected duration of the participants participation in the study: one and a half hour

20.Whom do I contact for further information

Dr. L. Aswathy
Post Graduate
Department of Physiology
SMIMS
Kulasekharam

Place : Kulasekharam **Signature of investigator**

Date :

CONSENT FORM

PART – II

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled Effect of Hypertension on Nerve conduction parameters in patients attending Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Name of the participant: **Address of the participant:**

Contact Number of the participant :

Signature / Thumb impression of the participant/Legal guardian

Witness

1.

2.

Date :

Place : Kulasekharam

8. Discussion

The present study was done to assess the effect of hypertension on increasing BMI and age in nerve conduction study variables in patients attending the outpatient Department of General Medicine.The clinical procedures were conducted at the research laboratory in the Department of Physiology at SreeMookambika Institute of Medical Sciences located at Kulasekaram, Kanyakumari district. This study was designed to assess the effect of hypertension on BMI and age on nerve conduction variables since there are very few studies done to correlate hypertension with peripheral neuropathy, with age and BMI as aggravating factors. In India hypertension is the third leading killer under category of non-communicable disease.[21]

8.1 BMI and Age:

136 participants of the study were categorized into two main groups Control group and hypertensive group.This grouping was further subdivided into various groups based on BMI and age. Table 7 represents mean calculation of height and BMI in various age groups.Case History was recorded for all the 136 participants to verify the inclusion and exclusion criteria.The basic data such as height and weight were recorded from which the BMI was calculated. Mean Height and

MeanBMI were standardized. Onesingle mean height was chosen for the entire study for all the group subdivisions.

Mean BMI was divided into four major BMI's falling in the normal range 19.5, Pre-obese 26.75,Obese Class I 31.5, Obese class II 35.6.This was achieved by following the classification of world health organization.[116] The age grouping was subdivided into two ranges 30-45 yrs covering the younger subjects, and 50-60 yrs covering the elderly subjects.

8.2 Blood Pressure:

Table 9a and 9b represents the blood pressure measurements in the age range 30-45 years and 50-60 years, mean BMI in both control subjects and hypertensive patients. In the control subjects there was significant statistical increase in the levels only in the age range of 50-60 yrs in the BMI 31.5(Group III C), and 35.6(Group III D).

This is in contrast with the hypertension subjects where significant changes in blood pressure occurs in the normal range BMI of 19.5 in age 30-45 years and the statistical peak significance occurs in Class II Obese (Group II D) in the range of 30-45 years.

8.3 Nerve conduction studies:

To assess the effect of hypertension on nerve conduction study variables along with BMI and age as co-factors; two motor nerves (Tibial and Common peroneal nerve) and two sensory nerves (Superficial peroneal and sural nerve) were studied in the control and hypertensive subjects.

Table 10a and 10b represents the Tibial nerve conduction studies.

In control subjects with age 30-45 years the statistical significance of latency and conduction velocity starts to decrease with BMI 31.5.It attains peak statistical significance with BMI 19.5 in the age group of 50-60 years and this peak statistical significance occurs in other BMI's of 26.5,31.5, 35.6 in the age group of 50-60 years.

In control subjects with age 30-45 years,the statistical significance of duration and amplitude attains statistical significant decrease in BMI 35.6.It also showed statistical significant decrease with BMI 31.5 and 35.6 in age 50-60 years.

In hypertensive subjects,with age 30-45 years,the onset of peak statistical significance of duration,latency, amplitude,conduction velocity occurs in BMI 35.6.

In hypertensive subjects with age 50-60 years,the peak statistical significance of duration, latency, amplitude, conduction velocity is attained with all BMI groups.

Table 11a and 11b represents the common peroneal nerve conduction study.In control subjects with age 30-45 years the statistical significance of duration,latency,amplitude,conduction velocity starts to decrease with BMI31.5 and also showed statistical significant decrease in BMI 35.6.

In control subjects with age 50-60 years the statistical significance of duration,latency,amplitude,conduction velocity occurs in all BMI groups of 19.5,26.75,31.5,35.6.

In hypertensive subjects ,with age 30-45 years,the statistical significance of duration,latency, amplitude ,conduction velocity is seen in BMI 26.75.The peak statistical significant decrease is obtained in BMI 35.6.This peak statistical significance is sustained in all BMI groups with age 50-60 years also.

Table 12a and 12b represents the superficial peroneal nerve conduction study.In control subjects with age 30-45 years the statistical significant decrease ofduration,latency, amplitude ,conduction velocity occurs with BMI 31.5.This significance is maintained with BMI 35.6 in the same age group.It attains peak

statistical significant decrease in BMI 26.75, 31.5, 35.6 in age group of 50-60 years.

In hypertensive subjects with age 30-45 years the statistical significance is attained with BMI 26.75.The peak statistical significance decrease of duration,latency,amplitude,conduction velocity is attained with BMI 31.5,35.6 in the same age group of 30-45 years.

In hypertensive subjects with age 50-60 years the peak statistical significant decrease ofduration,latency,amplitude,conduction velocity is obtained with BMI 26.5, 31.5, 35.6.

Table 13a and 13b represents the sural nerve conduction study.In control subjects with age 30-45 years the statistical significance ofduration,latency, amplitude ,conduction velocity attains statistical significance with BMI 31.5.This statistical significance is maintained withBMI of 35.6 in the same age group.Also thisstatistical significance is maintained in age 50-60 years with other BMI'S of 19.5, 26.5, 31.5, 35.6.

In hypertensive subjects with age 30-45 years the statistical significance of duration,latency,amplitude,conduction velocity is obtained with BMI 26.75.The peak statistical significance is obtained with BMI's 31.5, 35.6 in the same age group of 30-45 years.

In hypertensives with age 50-60 years peak statistical significance of duration,latency, amplitude, conduction velocity is obtained with BMI 19.5,26.5,31.5, 35.6.

Though certain papers report a negative association between hypertension and peripheral neuropathy[96,97], Our study presents a positive correlation between hypertension and peripheral neuropathy. However, there are studies that present a positive correlation between hypertension and nerve conduction studies by Dhafir. I El-Yassinet. al.[51] BMI and age related studies done by Awang et al[99] observed that with increasing BMI and age in control subjects there is slowing of nerve conduction velocity in median (both motor and sensory) nerve with increasing BMI and age.

Another study published in the Indian J. PhysiolPharmacol in 2012 by Pawar SM et al.[117] has also similar findings related to our study. They report prolongation of distal motor latency with increasing BMI. They also observed F-wave minimum velocity which was significantly prolonged in motor tibial nerve.

Dhafir I. El- Yassin[51] has clinically proved a positive correlation between hypertension and nerve conduction velocity and reports that patients with hypertension present peripheral sensory neuropathy mainly of axonal type with

demyelination as an secondary outcome only in the sural nerve.

In our study demyelination and axonal changes are observed as alterations in the nerve conduction study variables such as CMAP or SNAP latency and amplitude.The changes in hypertension occurs at a relatively earlier age range of 30-45 years with BMI 26.75. In the control subjects, the changes occurs in the same age range of 30-45 years butwith a higher BMI. These results are in agreement with Dhafir I. El- Yassin's paper.[51]

8.4 Molecular Pathophysiology Pertaining To Nerve Conduction Variables

Though we have a clear understanding that BMI and age can cause deficits in nerve conduction variables in control subjects; the presence of hypertension in a subject along the with age and BMI as co-factors could aggravate the deficits in nerve conduction variables at an earlier age when compared to control subjects thus making them prone to present with peripheral neuropathy.

Though our study has not included much pathophysiology experiments we were interested in finding a basic working on molecular pathophysiologic mechanism that would enlighten us on what is the process of BMI and age in reducing the nerve conduction variables.

We hypothesize that hypertension mediated dyslipidemia can cause oxidative stress that in turn imbalances Angiotensin II and vasodialator balance especially nitric oxide and endothelin-1. The process is continued as a feed forward mechanism since the antioxidant status is compromised due to oxidative damage to the antioxidant enzymes and the presence of high volume of free radicals being the primary culprits of oxidative stress.

Depletion of Nitric oxide is an outcome of oxidative stress which mediates the production of peroxynitrite a biological reaction of nitric oxide with single oxygen (free radical). The formation of peroxynitrite and free radicals and depletion of antioxidants mediate the activation of aging mechanisms such as senescence and apoptosis that culminate into axonal degeneration observed as CMAP or SNAP amplitude decrease with prolongation of duration in control and hypertensive subjects and this occurs at earlier stage in the hypertensive subjects. This is possibly due to onset of oxidative stress at an earlier stage and its non-depletion,despite various therapies targeted on hypertension.

Axonal degeneration or apoptosis of the nerve occurs as an outcome of oxidative stress mediated by Poly-ADP-ribose polymerase [PARP], an death enzyme present within the Axon.

Demyelination is an outcome of degeneration of myelin which is also achieved by oxidative stress implementing uncontrolled and irreversible lipid peroxidation causing the degradation of myelin which causes latency changes in the nerve conduction.

Finally the Na^+K^+ATPase at the nodes of Ranvier 0 also lose its functionality due to deprivation of ATP that is an outcome of inefficient mitochondrial functioning during the onset of Axonal degeneration.

All these processes finally culminate into functionally defective nerve, incapable of firing; and is witnessed clinically as peripheral neuropathy in the peripheral nerves in hypertension.

Crowley SD [118] and Yasunari K et al[119] have proved clinically that oxidative stress is an outcome of chronic inflammation in hypertensive subjects. The onset of oxidative stress in hypertensive subjects depletes the levels of nitric oxide via the formation of peroxynitrite. This mechanism has been clinically proved by Moriel P et al[120].

Peroxynitrite mediated activation of PARP has been experimentally been proved in spontaneously hypertensive rats by Dereset al.[121]. The association of PARP activity mediating axonal degeneration has been experimentally proved in a rat model of multiple sclerosis by Penberty WT and Tsunoda I[122]; and the presence

of axonal degeneration in hypertension has been proved experimentally in SHR rats by Sanada LS et al[123]. SHR rats are molecular mimics of essential hypertension and they serve as good counterpart in working the mechanisms behind essential hypertension that cannot be done in human subjects.

Our study clearly demonstrates, axonal degeneration as changes in CMAP or SNAP amplitude and prolongation in duration in control subjects with higher BMI and age, whereas, in the essential hypertensives changes occurred in lower age range with increasing BMI.

Demyelination was also observed as latency changes in our study following the same trend of onset in control and hypertensive subjects as indicated for axonal degeneration.

Our findings are supported by clinical studies of Henry C. et al[124], who has studied the effect of aging on sensory nerve conduction parameters and has presented that sensory nerve conduction velocity does change with aging.

Aging mechanisms have experimentally proved in hypertension by Kung CF et al[125]

Demyelination is observed as latency changes with increasing BMI and age which has been clinically proved by Awanget al[99] and experimentally it has been proved by Sanada LS et al.[123]

Figure.1 Mechanism of Oxidative stress Mediated Neurol degeneration in health and Disease

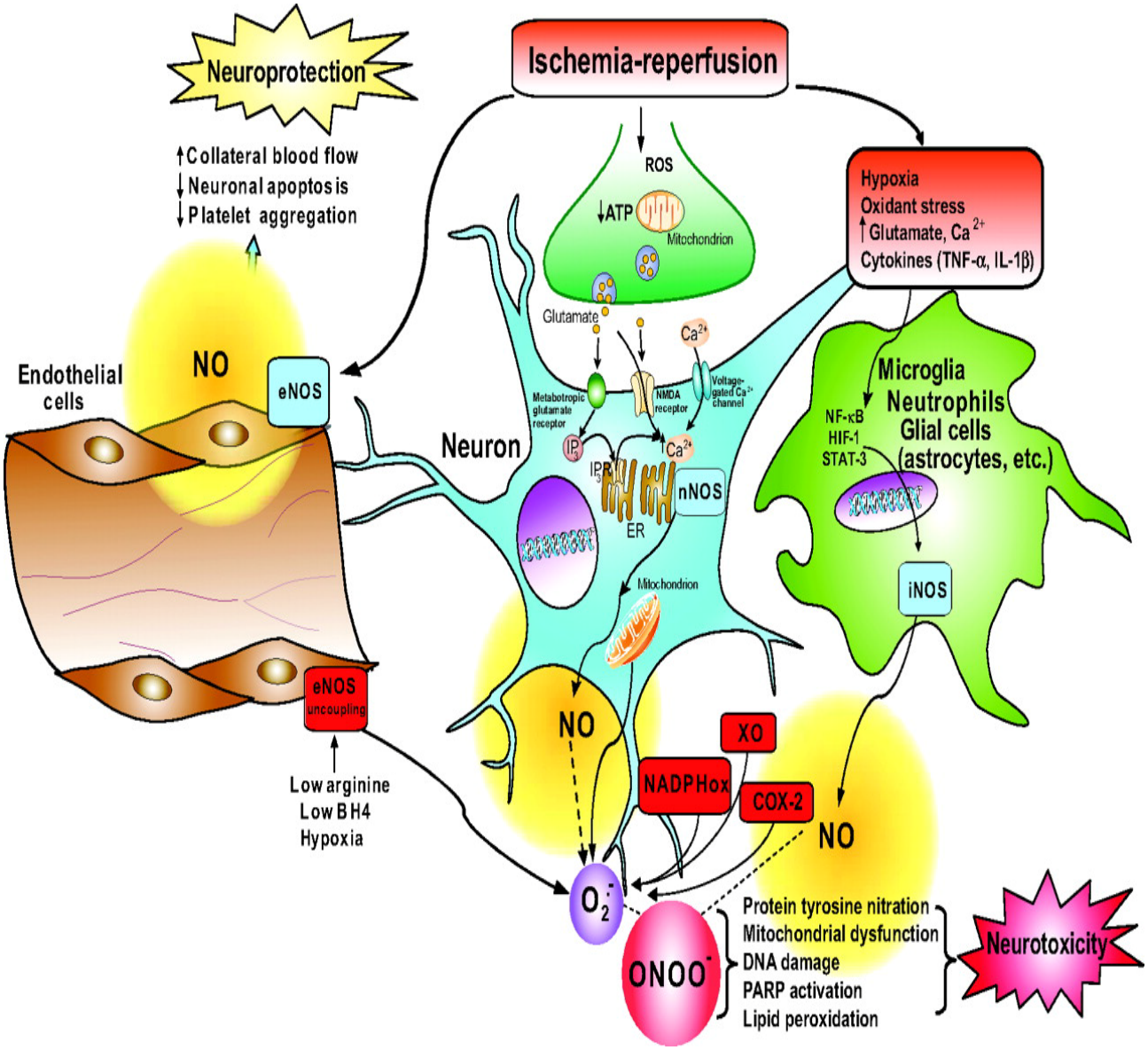

Image 1: Computerised RMS ALERON 401 EMG/NCV/EP System